Investigation Into the Reduction of Benzylidenephthalide Derivatives

A Senior Honors Thesis in the Department of Chemistry

Sweet Briar College

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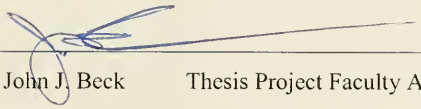
Awarded High Honors



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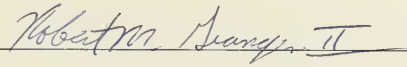

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Investigation Into the Reduction of Benzylidenephthalide Derivatives

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~ Abstract ~

Oshá is a medicinal herb used in various cultures to treat illnesses such as headaches, strokes, anemia, fever, and menstrual irregularities. The bioactive component in Oshá has been found to be *(Z)*-ligustilide. The specific site of reactivity related to the bioactivity of *(Z)*-ligustilide is C-8. The reactivity at C-8 has been related back to the compound's α,β.γ.δ-unsaturated lactone. SAR studies have been completed in order to synthesize a more bioactive compound than *(Z)*-ligustilide. The synthesis of these derivatives involves the addition of an aromatic alcohol moiety containing various R groups to the readily available compound phthalide. Phthalide contains an aromatic ring, thus reducing the effect of the α,β.γ.δ-unsaturated lactone. In an effort to enhance the effects of the α,β,γ,δ-system and make it more prominent Birch reductions were subsequently performed on the derivatives. The initial investigation into this procedure resulted in the decomposition of the derivative into phthalide and the corresponding aldehyde. This thesis addresses these problems and offers three Synthetic Schemes to afford the desired compound. Exploration of these Synthetic Schemes resulted in unsuccessful Birch reductions for all three Schemes, and the target compound was not obtained. However, the discovery of a key synthetic step may lead to the attainment of the 4,5-dihydrophthalide, and the discovery of various other methods that could lead to the target compound.

~ Acknowledgements ~

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~ Dedication ~

I would like to dedicate my thesis to my parents. You have constantly encouraged all of my endeavors and ambitions, and I am very grateful for that. You are the reason behind all that I have accomplished and without your backing I would never have attempted anything. Your faith in me means a lot and I would like to thank you for always believing in me and not letting me give up ☺

~ Table of Contents ~

Page Number

~ List of Figures ~

~ List of Schemes ~

~ List of Tables ~

~ List of Abbreviations ~

^{1}H – proton

^{13}C – carbon

δ^{+} – partial positive

DCC – 1,3-dicyclohyexylcarbodiimide

DEPT – distortionless enhancements by polarization

DIPA – diisopropylamine

DMAP – 4-dimethylaminopyridene

DMSO – dimethylsulfoxide

EDG – electron donating group

EWG – electron withdrawing group

HMDS – hexamethyldisilazane

HRMS – high-resolution mass spectrometry

HSQC – heteronuclear single quantum correlation

i-PrOH – isopropanol

LDA – lithium diisopropylamine

LUMO – lowest unoccupied molecular orbital

n-BuLi – *n*-butyllithium

NMR – nuclear magnetic resonance

nOe – nuclear Overhauser effect

SAR – structure activity relationship Studies

TEA – triethyl amine

THF – tetrahydrofuran

~ Introduction ~

Natural products chemistry refers to the study of medicines derived from plants. There are several popular medicines used today that have been discovered through herbal treatments in various cultures. Aspirin, also known as acetylsalicylic acid, is a common drug used that has been around for thousands of years (Figure 1).

Figure 1: The evolution of aspirin

The Greek physician, Hippocrates (*ca.* 460 B.C to 377 B.C.) prescribed the bark and leaves of the willow tree to help relieve headaches, pains, and fevers.[1] In 1829 scientists discovered that the bioactive compound in the willow tree was salicin.[2] Henri Leroux successfully extracted salicin in its crystalline form in 1829, and Raffaela Piria successfully converted salicin to salicylic acid in 1838.[2] Unfortunately, salicylic acid was considered too harsh on the stomach so a means to "buffer" it was investigated.[2] In 1899 Felix Hoffman discovered a solution to the problem by converting salicylic acid to acetylsalicylic acid by reacting salicylic acid with acetyl chloride.[2] Acetylsalicylic acid was less of an irritant than salicylic acid, and Hoffman convinced Bayer to market the item. On March 6, 1899 Bayer patented aspirin and today aspirin is used by over 80 million Americans.[1]

Another common class of compounds found in plants are flavonoids. Flavonoids are plant metabolites that have been found to possess antioxidant activity in addition to

having affects against cancer and the immune system. Catechins (Figure 2) are a class of flavonoids that are of specific interest because they comprise one-fifth of the 1 g/day total intake of flavonoids in the United States.

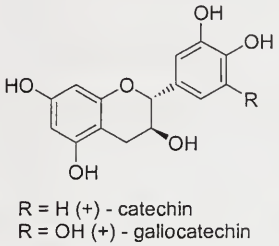


Figure 2: Catechins: A class of flavonoids

Catechins are found in many fruits and vegetables, but they are the principle components in tea and comprise 30-42% of green tea solids. Studies have shown that consumption of green tea may reduce risk of certain cancers, coronary heart disease, and stroke.[3] Studies have also been conducted on various fruits and vegetables in order to determine which ones would be effective in the prevention of cancer. Catechin content was found to be high in apples such as Golden Delicious and Granny Smith, but the opposite proved true for pears, kiwi fruit, and peaches. Chocolate was also found to have high amounts of catechins present, but dark chocolate had more. The final results of this study showed that certain fruits had catechin content, whether it was high or low, but vegetables did not. It is hopeful that research concerning catechins can lead to the treatment of chronic diseases.[3]

In 1963 extracts from the bark of the Pacific Yew showed cytotoxic and antileukemic activity, and in 1971 the compound found to be the bioactive component was paclitaxel, commercially known as Taxol®[4] (Figure 3).

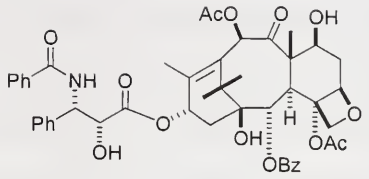


Figure 3: Taxol®

After exhibiting activity against breast cancer and melanoma, the National Cancer Institute allowed the investigation of Taxol® as an anticancer agent.[4] However, a substantial obstacle was encountered in the isolation of Taxol® from the Pacific Yew, which was initially being extracted with a 0.014% yield.[4] After Taxol's initial testing showed it to be active against breast cancer and solid tumors, Taxol® was given to Bristol-Myers Squibb to synthesize. After facing various difficulties in the synthesis of Taxol® and supply problems, the first total synthesis of Taxol® was accomplished simultaneously by two groups in 1994, however both sytheses produced low yields.[5,6] In 1996, a high yielding semisynthetic process for the production of Taxol® was found.[4] Various studies are being conducted today to discover a high yielding total synthetic process of Taxol®. Today, Taxol® is the leading anticancer drug and has become the best selling anticancer drug in history.[4]

As the three examples noted above suggest, a plant or medicinal herb found to be active against an illness goes through the process of having the bioactive component isolated from the plant, characterized, synthesized, and in the case of many molecules subjected to structure-activity relationship (SAR) studies.

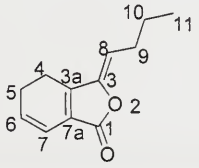
One type of isolation process, called bioactivity-directed fractionation, starts with the extraction of the plant by either successive solvent extractions or the use of a soxhlet continuous extractor. After the plant material has been extracted, the crude extract

material is subjected to a liquid/liquid partition; one method for separating molecules based upon their polarity; non-polar, polar, very polar. All layers are checked for bioactivity, and the bioactive layers are subjected to further isolation methods until compounds are isolated and tested for specific bioactivity. Once the bioactive compounds in a plant have been isolated, they can be characterized via nuclear magnetic resonance (NMR) spectroscopy and high-resolution mass spectrometry (HRMS). The synthesis of novel bioactive molecules is typically performed to alleviate the dependence of acquiring plant material for the product. If the synthesis of a new compound is to be undertaken, a retrosynthetic analysis is performed and the total synthesis of the target molecule is undertaken. If the reactive site of a bioactive molecule is known, an SAR study may be initiated to determine if the activity of the analogs can be enhanced relative to the parent molecule.

Many plants have been used for illnesses ranging from the common cold, to mental illness, to cancer. A common example is *Ligusticum porteri*, from the family Apiaceae. *Ligusticum porteri* has various names in different cultures; Hispanic residents of Rio Grande know it as "chuchupate," but it is more commonly referred to as Oshá.[7] Oshá is perennial herb that is characterized by its thick rhizome and strong odor.[8] Oshá can be found in the southwestern United States, Mexico and South America and is predominately used in the Orient, Native American, Hispanic, and European cultures.[9] Ritual practices with Oshá include carrying a piece of rhizome to ward off snake bites and witches, and bring good luck.[8] It is also believed in certain cultures that taking the root once a day will keep one young.[7] Tea made from the dried roots of Oshá has been used to alleviate stomachaches, colic, ulcers, and diarrhea. Powdered roots have been

applied to wounds as a way to prevent of infection.[8] Oshá has also been used to treat illnesses such as the common cold, anemia, headaches, stroke, and menstrual irregularities.[8]

Studies have isolated and characterized the bioactive component in Oshá and have identified it as *(Z)*-ligustilide, **1**.[10] *(Z)*-ligustilide has shown antiviral, antibacterial, and antifungal activity.[7] One specific site of reactivity with biological macromolecules has been found to be at C-8 (Figure 4).



1

Figure 4: *(Z)*-Ligustilide and its numbering

(Z)-Ligustilide's bioactivity has been related to its conjugated lactone system. Compound **1** has been shown to contain a number of reactive sites, which may be involved in a variety of processes such as 4+2 and 2+2 cycloadditions, as well as 1,2-, 1,4-, or 1,6-nucleophilic addition. Figure 5 shows the general reactivity of **1**.

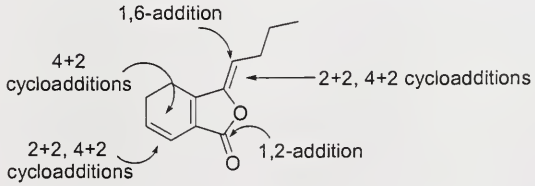
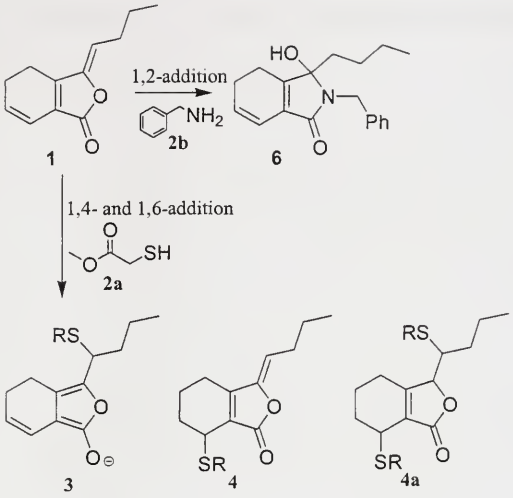
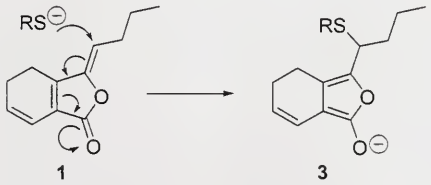


Figure 5: General reactivity of 1



Scheme 1: Hard/Soft acid and base concept

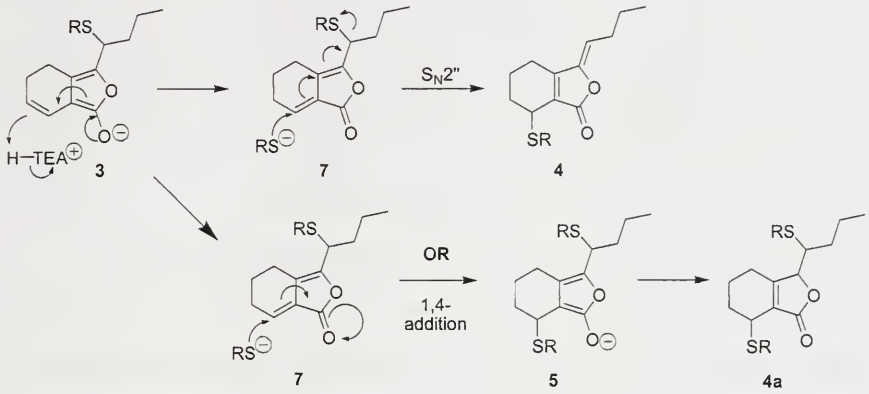
In a previous study, *(Z)*-ligustilide was reacted with the sulfur nucleophile, methyl thioglycolate, compound **2a**, and with the nitrogen nucleophile, benzylamine, compound **2b** (Scheme 1). Compound **2a** is a model reactant used to mimic other biologically relevant nucleophiles.[11] The presence of the α,β,γ,δ-system has been related to *(Z)*-ligustilide's bioactivity with C-8 being the purported active site for 1,6-addition (Scheme 2).



Scheme 2: 1,6-addition to 1

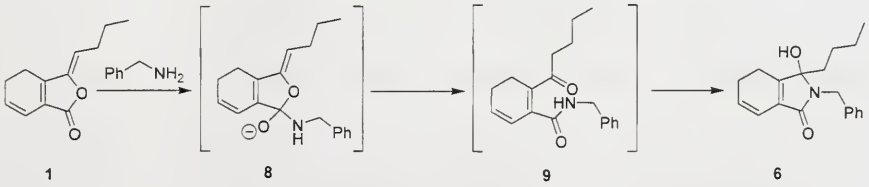
1,6-addition of **2a** results in enolate **3**. The collapse of the enolate and rearrangement in compound **3** affords the products of 1,4 addition, **4** and **4a** (Scheme 3).

Studies have found that **4a** is not a product of true initial 1,4-addition, but rather a product of 1,6-addition followed by 1,4-addition.[11]



Scheme 3: 1,4-addition to 1

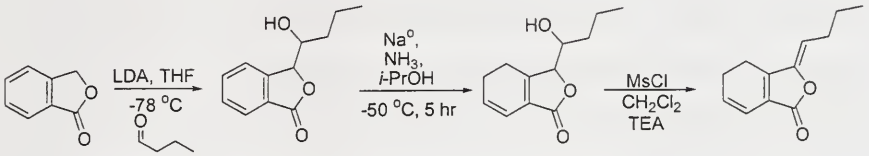
Compound **2b** was found to go through 1,2-addition with *(Z)*-ligustilide (Scheme 4). The difference in reactivity between **2a** and **2b** is consistent with Pearson's hard/soft acid and base theory.[12] The softer base, **2a** reacted with the softer electrophilic site on the molecule, the δ-position C-8 at the end of the conjugated lactone system. The smaller, more electronegative base, **2b**, reacted with the harder position, the carbonyl carbon.[11]



Scheme 4: 1,2-addition to 1

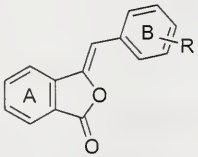
SAR studies have been performed on **1** in an effort to synthesize a series of molecules that will be more bioactive than **1**.[13] A more efficient method was discovered

than a previous report[14] for the synthesis of **1**. This improved methodology was then applied to the synthesis of its derivatives (Scheme 5).[13]



Scheme 5: Synthetic scheme of 1

The overall goal of the SAR studies of **1** was to make C-8 more reactive, therefore increasing the bioactivity of the analogs relative to **1**. With evidence showing C-8 to act as an electrophile, efforts were initiated to discover a way to affect the electron density at that position. This idea was substantiated by a separate study that showed the simple aromatic version of **1**, benzylidenephthalide, (**10a**, Figure 6), possessed bioactivity, thus supporting the concept of reactivity at C-8 being the site of bioactivity.



a R = H
b R = *para*-NO_2
c R = *meta*-NO_2
d R = *para*-Br
e R = *para*-Cl
f R = *para*-CN
g R = *para*-CF_3
h R = *para*-Me
i R = *meta*-Me
j R = *para*-OMe
k R = *para*-OH

Figure 6: Benzylidenephthalide, 10a, and derivatives

Although **10a** is a readily available compound, the ability to synthesize **10a** via the synthetic conditions for **1** was important for several reasons. **10a** sustained bioactivity, albeit less than **1**, through the replacement of the aliphatic side chain with an aromatic ring. The addition of the aromatic ring allowed for further conjugation to C-8, in addition to the conjugation with the lactone moiety. This also allows for further studies of aromatic rings containing R groups that were expected to affect the reactivity at C-8.

The drop in bioactivity of **10a** relative to **1** can been attributed to the aromaticity of ring A (refer to Figure 6, p. 8). As discussed earlier, the reactivity and bioactivity of **1** has been traced back to its α,β,γ,δ-unsaturated system. In Figure 7, it is shown that a 1,6-addtion of a nucleophile to **10a** would result in the dearomatization of ring A. The break in aromaticity and subsequent loss of stability of ring A makes 1,6-addition less likely to **10a**, thus resulting in a decrease in bioactivity in **10a** relative to **1**.

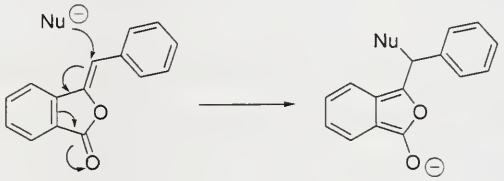


Figure 7: 1,6-addition to benzylidenephthalide

The compounds in the SAR study mentioned previously were to take advantage of the conjugation between the aromatic ring B and C-8. The various compounds only differed by the R group on ring B. To provide further correlation between R groups and their influence on C-8, results from a study done by L. P. Hammett were used to determine which R groups would be utilized in the SAR study. Hammett's equation resulted in the free energy relationship of mechanisms in his work involving the ionization of substituted benzoic acids. Hammett found a linear correlation in the reaction rates of substituted benzoic acids. If the substituent is placed far away from the reactive site to avoid steric problems, then the electronic effects of the substituent on the compound will diminish. The idea behind following Hammett's equation is to find a linear correlation between the reaction rates of benzylidenephthalide derivatives and the substituted benzoic acids. If Hammett's equation holds true then the amount of electron

density at C-8 should be influenced in direct correlation to the free energy ionization of the benzoic acid derivatives. In his original studies, completed in 1937, Hammett used p-NH_2, p-OMe, m-NH_2, p-Me, H, p-Cl, m-NO_2, p-NO_2 (increasing in acidity of derivatives) as the benzoic acid derivatives.[15] Ultimately, to obtain a larger variation and accommodate more substituents, final derivatives to be synthesized were selected from a study similar to Hammett's, published in 1979, but included more benzoic acid derivatives.[16]

Using Hammett's results compounds **10b-k** (refer to Figure 6, p. 8) were chosen to be synthesized where R was an electron withdrawing group (EWG), **10b-g**, or an electron donating group (EDG), **10h-k**. A study of the lowest unoccupied molecular orbital (LUMO) at C-8 was completed via molecular modeling in order to predict which compounds would be more reactive and thus overall more bioactive. A larger LUMO inferred that more electron density was being pulled away from C-8. Evaluation of the resonance structures and inductive effects of compounds **10a-k** suggest the EDGs should inhibit any nucleophilic addition to C-8 by increasing the amount of electron density at that position. In contrast, the EWGs are expected to activate C-8 by decreasing the amount of electron density at this site, and/or destabilizing the already present partial positive (δ^+) from the enone system.

Electron density for each molecule was mapped onto the LUMO to provide qualitative and quantitative data for C-8. The quantitative data was determined by mapping the LUMO of the compounds with an isovalue of 0.002 e/au^3, which allowed the calculation of LUMO size at each atom. Quantitative data results are given in Table 1.

	Compound															
Atom	1	10a	10h	10j	10k	10b	10c	10g	10f	10d	10e	12	13	14	15	16
1	0.02	0.022	0.019	0.017	0.018	0.016	0.009	0.019	0.014	0.017	0.018	0.032	0.025	0.017	0.019	0.02
2	0.001	0.002	0.002	0.002	0	0.003	0.001	0.002	0.002	0.002	0.001		0.001	0	0	0
3	0.013	0.017	0.012	0.014	0.012	0.018	0.015	0.014	0.016	0.015	0.014	0.005	0.014	0.015	0.021	0.011
3a	0.026	0.015	0.023	0.02	0.02	0.02	0.015	0.018	0.016	0.018	0.017	0.03	0.034	0.033	0.031	0.024
4	0.003	0.01	0.006	0.011	0.007	0.008	0.011	0.009	0.01	0.012	0.011					0.006
5	0.006	0.013	0.017	0.017	0.017	0.011	0.014	0.015	0.012	0.015	0.016					0.021
6	0.019	0.014	0.017	0.017	0.017	0.013	0.016	0.016	0.015	0.017	0.017				0.021	0.019
7	0.013	0.005	0.001	0.003	0.003	0.001	0.001	0.003	0.002	0.001	0.003				0.013	0.01
7a	0.029	0.014	0.015	0.015	0.017	0.017	0.018	0.013	0.013	0.015	0.019	0.021	0.032	0.003	0.031	0.029
8	0.022	0.021	0.022	0.022	0.017	0.014	0.021	0.02	0.02	0.022	0.022	0.026	0.025	0.026	0.023	0.021
9	0.002	0.01	0.008	0.008	0.008	0.016	0.01	0.015	0.01	0.012	0.01					
10	0.003	0.009	0.011	0.009	0.009	0.01	0.015	0.009	0.01	0.01	0.01					
11	0.002	0.006	0.005	0.005	0.003	0.014	0.008	0.01	0.008	0.009	0.009					
12		0.011	0.012	0.012	0.012	0.013	0.018	0.013	0.015	0.012	0.012					
13		0.003	0.002	0.002	0.002	0.012	0.008	0.007	0.008	0.003	0.003					
14		0.009	0.009	0.012	0.011	0.011	0.009	0.012	0.01	0.012	0.012					
15			0.001	0.002	0.001	0.016	0.007	0.015	0.01	0.004	0.004					
16				0.002		0.008	0.003	0.002	0.008							
17						0.008	0.003									

Table 1: LUMO values of molecular models calculated at an Isovalue of 0.002 e/au^3

To provide background information on the α,β,γ,δ -unsaturated lactone moiety of 1 and the targeted synthetic analogs, five fundamental compounds of increasing complexity were first modeled (Figure 8).

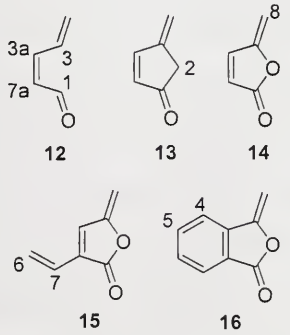


Figure 8: Molecules used to model the enone

Adhering to the same numbering scheme used for **1**, evaluation of Table 1 for the model systems, **12-16**, reveals some basic information regarding conjugated enones. As expected, the LUMO values for **12** corroborate with resonance theory at positions 1, 3a and 8. It was interesting to note that the addition of the oxygen at position 2 decreases the LUMO values significantly at position 1 for compounds **14**, **16**, thus confirming the stabilizing effect of the lactone oxygen on the carbonyl carbon. This affect was not noticed when a methylene moiety was inserted at position 2 (compound **13**). Another important feature to note was the large decrease in LUMO size of position 3a relative to compounds **12-15** when Ring A was aromatized, compound **16**. This is congruent with the theory of aromatic stability. However, the values of position 3 and 8 for compound **16** were smaller and more consistent with those of **1**. The models provided information for the conjugated lactone, both with and without, an aromatic system at the α,β position of the enone.

Analysis of the SAR analogs in Table 1 proved to be more complex. With the exception of compounds **10k** and **10b**, the most notable characteristic for the analogs was the absence of variation at position C-8. At this time, no explanation can be offered for the unusual LUMO values for position C-8 of compounds **10k** and **10b**. The position C-8 LUMO value for compound **10k** would be what was expected; yet no other EDG analog yielded a similar lowering. The low LUMO value at position C-8 for compound **10b** is what would be expected for an EDG, not the *para*-nitro analog. With these unusual results for **10k** and **10b**, it was expected that the difference in electronic nature of the substituents would provide more variation for the other C-8 LUMO values. These results were not consistent with bioactivity studies. A larger LUMO as expected with the

EWGs, but not seen, would have indicated that the compound would more reactive and therefore more bioactive, the converse was expected to happen with the EDGs.

The expected variations in LUMO values are seen at positions C-9, C-11, and C-13 for compounds **10j** and **10b**. As a resonance electron donor, the methoxy derivative, **10j**, places electron density at the C-9, C-11, and C-13 positions (Figure 9). This electron density is interpreted as a smaller LUMO value in Table 1, with position 9 being slightly larger due to purported distance from the substituent. Conversely, the resonance structure for compound **10b** (Figure 9) would translate to a larger LUMO value at the respective positions. Information in Table 1 for all analogs is congruent with the resonance structures of Ring B and the substituent.

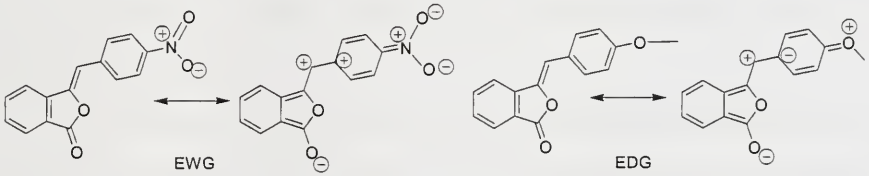


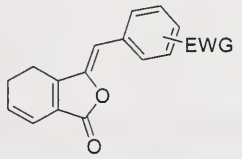
Figure 9: Resonance structures of compounds containing EWGs and EDGs

Evaluation of position 3a for compound **1** shows a relatively large LUMO value. Although a small decrease in LUMO values at this position were expected with the analysis of an aromatic Ring A, the large decrease in the EWG analogs was not anticipated; particularly when compared to the EDG analogs. For a full report of results refer to ref. 17.

Due to the inconclusive results of the molecular modeling study, the expected affects of an EWG and EDG were taken into higher consideration than the molecular modeling results. Per resonance structures, the EWGs, compounds **10b – g**, are expected to pull electron density away from C-8, and make it less stable and more reactive by

placing a positive charge next to a second positive charge (Figure 9). Overall, the increase in reactivity should affect bioactivity of the EWG derivatives by increasing them compared to the bioactivity of benzylidenephthalide. In order to show that the increase in bioactivity of these molecules is due to the EWG, the converse is expected with the EDG compounds **10h – k**. EDGs are expected push electron density to C-8, therefore making the site more stable and less reactive (Figure 9). It is expected that this increase in stability will lead to C-8 being less susceptible to nucleophilic attack, therefore decreasing the bioactivity of the EDG derivatives compared to that of **10a**. Internal studies have shown bioactivity results for the *(E)*-isomer of **10h**, **10g**, **10d**, and the *(Z)*-isomer of **10b** against *Staphylococcus aureus*.[18] The *(Z)*-isomer of **10b** has also shown activity against *Bacillus subtilis*, along with a *(E/Z)*-racemized mixture of **10b**, and mostly *(E)*-isomer of **10b**.[18]

To reiterate, the main goal of this project was to synthesize a compound that will be more bioactive than **1**. The investigation of aromatic phthalide side chain derivatives although successful, did not afford the high level of bioactivity sought. Therefore a study was undertaken to synthesize analogs containing an aromatic side-chain, by removing the π bond between C-4 and C-5, compound **17** (Figure 10). To achieve this goal it was thought that the easiest way to approach this synthesis was via Birch reductions.



17

Figure 10: Target compound desired after Birch reductions

Under normal Birch conditions, a phenyl ring containing an R group placed under standard Birch conditions will normally result in a 1,4-diene where an EWG will be at the C-3 position and an EDG will be at the C-1 position. A 1,4-diene forms with an EWG at the C-3 position because of the EWG's ability to stabilize the negative charge that forms during the reaction. An EWG favors protonation at the para-position, and the second protonation takes place at the center carbon[19] (Figure 11).

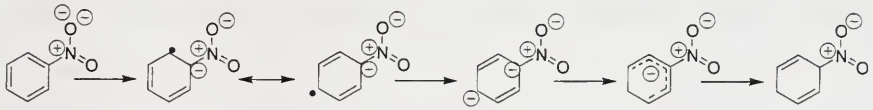


Figure 11: Birch reductions on EWG derivatives

A phenyl group containing an EDG promotes 1,4-dienes with the EDG at the C-1 position. An EDG is at the C-1 position in order to avoid interaction with the negative charge, which would result in destablization of the compound that would form (Figure 12). An EDG favors protonation at the ortho-position, and then at the center carbon of the hexadiene that forms with the addition of the second electron.[19]

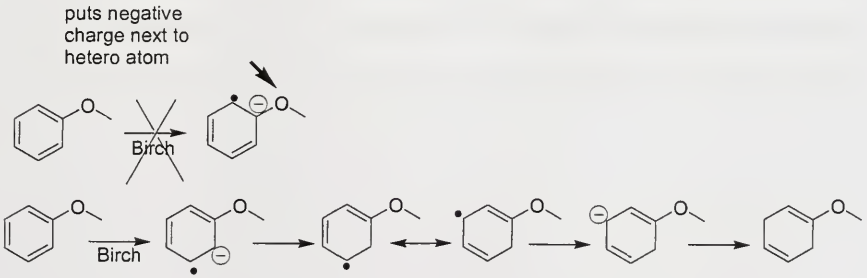
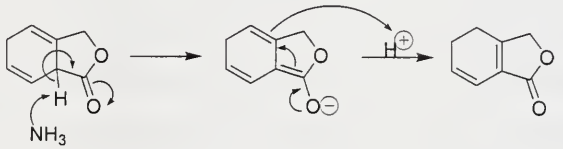


Figure 12: Birch reductions on EDG derivatives

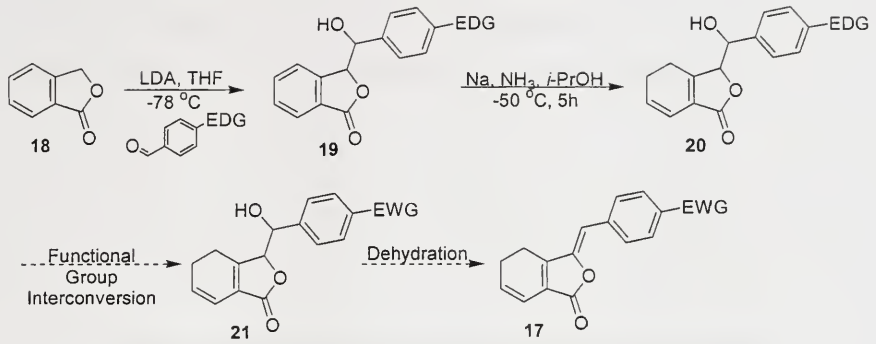
For compound numbers **10b-g**, the carbonyl at C-7a is an EWG, when observing the 1,4-diene during the Birch, the EWG should be on the third carbon. Interestingly, in

the synthesis of **1**, the 1,4-diene is not observed, and the 1,3-diene is obtained as the final product. Rearrangement to the 1,3-diene did not negatively affect the project because, as seen in **1**, the 1,3-diene is the arrangement needed. A possible explanation for the rearrangement of the 1,4-diene to the 1,3-diene is the extremely basic condition the compound is exposed to. The basic conditions could result in deprotonation of the α carbon and subsequent rearrangement to a more stable conjugated system, followed by exposure to acidic conditions protonating the compound to give the 4,5-dihydro molecule (Scheme 6).



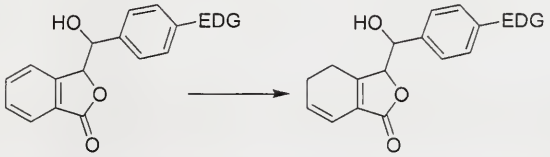
Scheme 6: Rearrangement of the 1,4-diene to the 1,3-diene

In the reduced analogs, **17b-g**, C-8 will have more facile conjugation with the 1,6-system, and with the aromatic ring containing an R group. The expectation behind the increased conjugation is that C-8 will be more reactive than in **1**, therefore more bioactive overall. Scheme 7 shows the synthetic scheme initially performed in an attempt to obtain **17**.



Scheme 7: Synthesis of target compound 17 containing an EWG

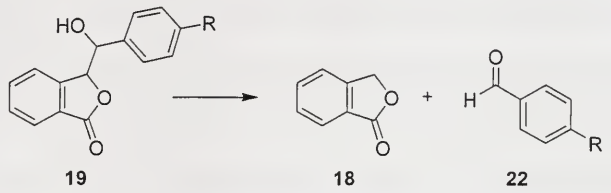
The reduction was performed following standard Birch reductions on an EDG derivative. The Birch reductions were done to EDG compounds in an attempt to affect only ring A. As previously shown in Figure 9 (p.13), the EWGs will pull electron density out of ring B, therefore making both ring A and ring B susceptible to the Birch reduction. An EDG would push electron density into ring B, therefore deactivating it during the Birch reduction thus leaving ring A susceptible to the reduction, which was the desired result (Scheme 8).



Scheme 8: Desired result from Birch reductions on EDG derivatives

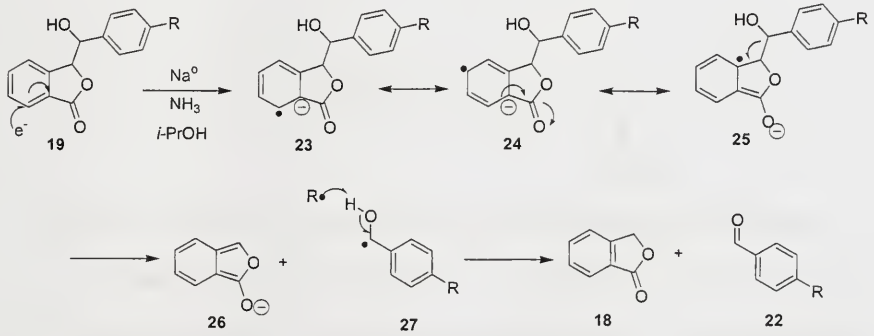
It was thought that the EDG would sufficiently deactivate ring B and the carbonyl of the phthalide lactone would serve to activate ring A, therefore, allowing only the reduction of ring A to obtain the target compound. Unfortunately, an unforeseen problem

in the Birch reduction was that instead of removing the bond at C-4 and C-5, the compound decomposed into the corresponding starting materials (Scheme 9).



Scheme 9: Decomposition of compound 19 during Birch reduction

The presence of two benzyl groups within **19** may offer a plausible explanation for decomposition. Scheme 10 offers a possible mechanism to explain the decomposition of **19**.

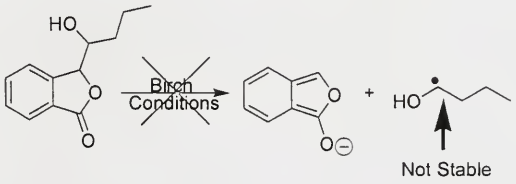


Scheme 10: Plausible explanation of the decomposition of compound 19

Initially, under Birch conditions, a radical anion is formed in the phthalide moiety of compound **19** to generate compound **23**. Although not typically seen, compound **25** can be a product of resonance. Compound **25**, although not desired for the formation of the target molecule, is a very stable and viable intermediate. The radical is stabilized by a tertiary carbon, and the electron pair at C-7a is stabilized through conjugation with the carbonyl as shown. The resonance stabilized compounds, **26** and **27**, promote cleavage

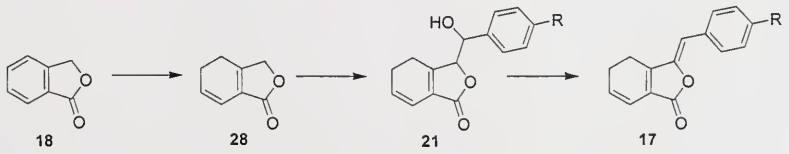
between C-3 and C-8, therefore facilitating the decomposition of **25**. In the formation of the enolate, compound **26** is aromatic, while the radical in compound **27** is stabilized by the aromatic ring with an EDG. Compound **22** forms by the abstraction of a hydrogen atom in **27**, and **18** is formed from **26** during the acidic work up of the reaction.

The synthesis of *(Z)*-ligustilide did not result in decomposition into phthalide and aldehyde, which can easily be explained by the instability of a radical on the butyl group (Scheme 11). Concerning the benzylidenephthalide derivatives, benzylic position radicals are very stable,[20] but for *(Z)*-ligustilide there is no benzylic position radical that forms if the compound were to decompose, which implies that if the compounds are not stable then there is no reason for the molecule to break apart.



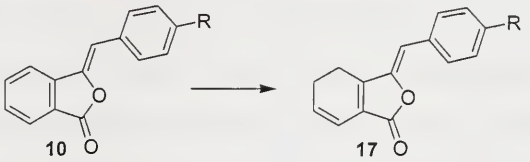
Scheme 11: The stability of 3-hydroxybutylphthalide during Birch reductions

To continue the goal of synthesizing a compound more bioactive than **1**, this thesis addresses the problem of obtaining the reduced derivatives. Several methods have been investigated in hopes of synthesizing the 4,5-dihydrobenzylidenephthalide derivatives. The first proposed Synthetic Scheme reduces **18** and then the aromatic moiety will be added to the molecule (Scheme 12).



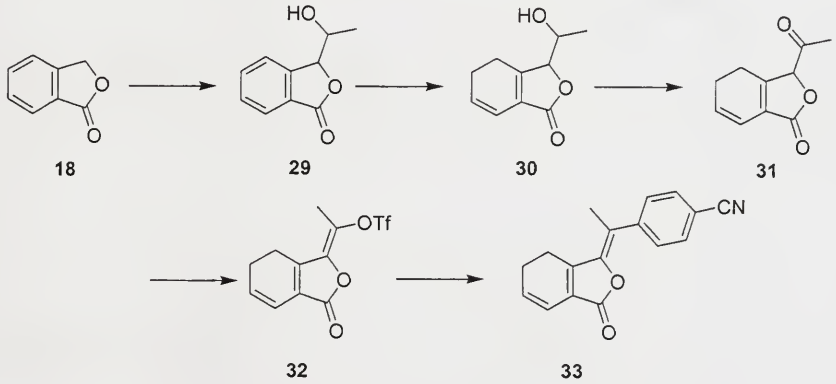
Scheme 12: Synthetic Scheme 1

Synthetic Scheme 2 is the proposed reduction of compound **10** rather than the alcohol moiety as previously attempted (Scheme 13).



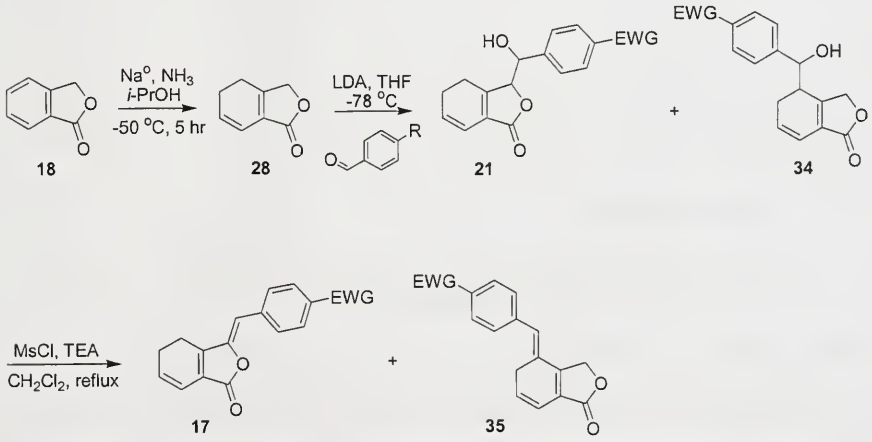
Scheme 13: Synthetic Scheme 2

Synthetic Scheme 3 is a novel approach in the synthesis of the reduced derivatives (Scheme 14).



Scheme 14: Synthetic Scheme 3

In an attempt to obtain target compound **17**, research on the three proposed Synthetic Schemes was implemented. Synthetic Scheme 1 in essence is the reverse of previous synthetic attempts, Scheme 5 (p. 8) and Scheme 7 (p. 17). To alleviate the problem of decomposition of **20**, Synthetic Scheme 1 was investigated. Synthetic Scheme 1 addressed the decomposition of **20** by initially performing the Birch on **18** then continuing the synthesis (Scheme 15), therefore the compound subjected to Birch reduction is not likely to decompose and the obstacle faced in previous syntheses is evaded.



Scheme 15: Synthetic Scheme 1 with proposed initial conditions

A concern regarding the Birch reduction on compound **18** was the opening of the lactone ring. The harsh conditions of the Birch could result in the cleavage of the lactone ring to produce methylbenzoate.[21] Literature procedure shows that lactone cleavage of compound **18** will not be the major product due to phthalide being coplanar.[21] Phthalide's coplanar characteristic does not provide the optimal geometry needed for the

cleavage to take place. What is required is that the π system of the carbonyl carbon and lactone oxygen be orthogonal to the aromatic ring in order for the cleavage to occur.[21] Since it is very unlikely for compound **18** to decompose under Birch conditions it is feasible to obtain the 4,5-dihydro product. Successful reaction of **18** under modified Birch conditions can provide compound **28**, and then be taken on to step 2, the addition of the aromatic moiety. Initially in step 2, Lithium diisopropylamine (LDA) is used to generate the phthalide anion. Although, H-3 is the most acidic hydrogen on **18**. There is uncertainty with regards to compound **28** as to whether H-3 or H-4 is the more acidic hydrogen. Both are γ hydrogens, and deprotonation of either carbon would result in formation of an enolate (Figure 13).

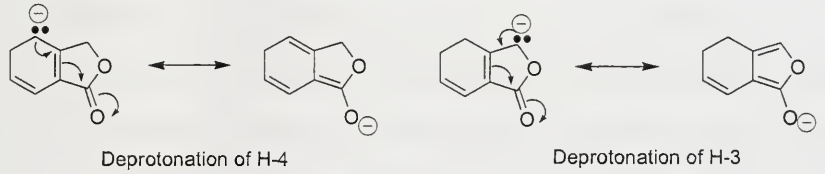


Figure 13: Enolate formation from the deprotonation of H-3 or H-4 of 4,5-dihydrophthalide

Proton (^{1}H) NMR data shows H-3 to be more downfield, thus indicating a more acidic hydrogen. In order to obtain the target molecule, C-3 must be deprotonated to give compound **20**, but compound **34** is also viable as a potentially bioactive compound. The third and final step of Synthetic Scheme 1 is the dehydration of compound **20** or **34** to obtain the target compound, **17,** or compound **35**. Compound **35** is just as acceptable as compound **17** because it maintains conjugation of the α,β,γ,δ-system (Figure 14) which, as stated previously, is related to the bioactivity of **1**.

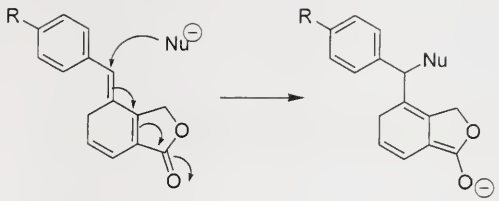


Figure 14: The α,β,γ,δ-unsaturated system in compound 35

The Birch reduction of **18** did not provide optimum yield even though various conditions were attempted (Appendix (A)-35). In order to determine if the reduced product was obtained, chemical shifts seen in **1** were compared to the ^{1}H NMR data of the crude mixture. The two initial peaks looked for were H-6 and H-7. In *(Z)*-ligustilide, both H-6 and H-7 appear as a doublet of triplets at 5.98 and 6.26 ppm, respectively.[11] Proton NMR data of crude material, 85% yield, (A-01) indicates that the Birch reduction to afford **28** may have been successful. The distinguishable splitting of H-6 and H-7 was visible and prompted the purification of the crude material. Various eluent systems were tested for separation including hexanes/EtOAc (1:1, 1:2, 1:6, 1:9), hex/EtOAc/$CHCl_3$ (1:2:1, 1:2:2, 1:2:3, 1:3:2, 1:4:2, 2:3:2, 2:2:1), and acetone/pet. ether (1:3). As seen in Figure 15 the TLC of the crude material run in 1:2:1 hex/EtOAc/$CHCl_3$ shows clear separation of spots indicating that isolation of **28** should be successful, however various attempts at separation of the product from starting material proved to be ineffective via column chromatography and preparatory plates.

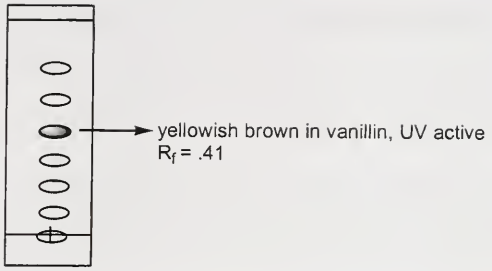
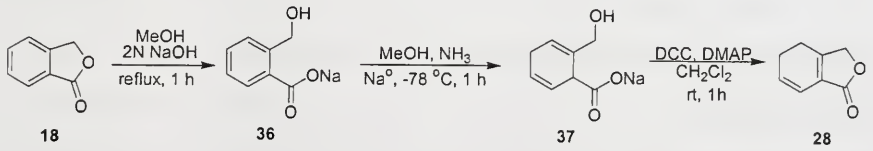


Figure 15: TLC of crude material of compound 28

As seen in the purified product (10% yield, A-02) phthalide was still present at a 1 to *ca.* 13.5 starting material to product ratio. All attempts to separate **18** and **28** proved to be futile indicating the possibility of **18** and **28** co-eluting. Due to the unsuccessful isolation of **28**, time constraints, and low-yielding results, further investigation of Synthetic Scheme 1 was temporarily discontinued.

During the investigative process, an alternate method was discovered that closely paralleled Synthetic Scheme 1. The method offered another approach that would provide compound **28** (Scheme 16).[22]



Scheme 16: Reduction of phthalide after lactone opening followed by ring-closure

This synthesis successfully reduced phthalide to obtain the 4,5-dihydro product by initially opening up the lactone, compound **36**. Hydrolysis of phthalide provided quantitative yield as seen in the ^{1}H NMR (A-03). The ^{1}H NMR (A-04) integrates to the expected 7 hydrogens, and the carbon 13 (^{13}C) NMR (A-06) showed the presence of the 8 carbons in the compound. In the DEPT (distortionless enhancements by polarization

transfer) 135, the disappearance of 3 peaks confirmed the presence of 3 quaternary carbons. The DEPT 135 also confirmed the presence of 1 methylene (methylene peaks show (-) enhancement in a DEPT 135), and 4 methynes. Although acid/alcohols in this configuration are usually extremely facile to ring closure,[20] the stability of the carboxylate does not allow for the alcohol moiety to attack C-1 and thus form the lactone. The benzyl alcohol/acid was then subjected to Birch conditions to obtain the 1,4-diene, compound **37**. Because compound **37** produced the typical 1,4-diene, 3 alkene signals were sought, H-4, H-6, and H-7. The ^{1}H NMR of the crude Birch material (45% yield, A-07) contained the alkene signals sought and integrated to the expected 3 hydrogens. Purification of the product via recrystalization in a 1:1 hex/EtOAc mixture provided a tan solid at a 21% yield (low yield due to inadequate extraction during workup). As seen in A-08, the alkene signals did appear at proper chemical shifts, 5.85 - 5.88 ppm for H-4 and H-6, while H-7 appeared slightly upfield at 5.77 – 5.80 ppm due to the carboxylate group. H-3 had a chemical shift upfield compared to **18**, due to the added electron density of the alcohol group (3.99 – 4.07 vs. 5.3 ppm), and H-5 appeared in the vinyl region at 2.72 – 2.72 ppm. Carbon-13 and the DEPT 135 NMR of this compound also confirmed that the isolated compound was **37** with the required 8 carbons, 2 of which are methylenes and 2 quaternary carbons. An nOe (nuclear Overhauser enhancement) (A-11) was performed in order to confirm proton assignments. As seen in Figure 16, the proton anticipated to be H-5 was irradiated and enhancements observed at proton peaks belonging to H-4 and H-6 indicated the proton assignments were correct; some long-range coupling to H-7 and H-3 were also observed.

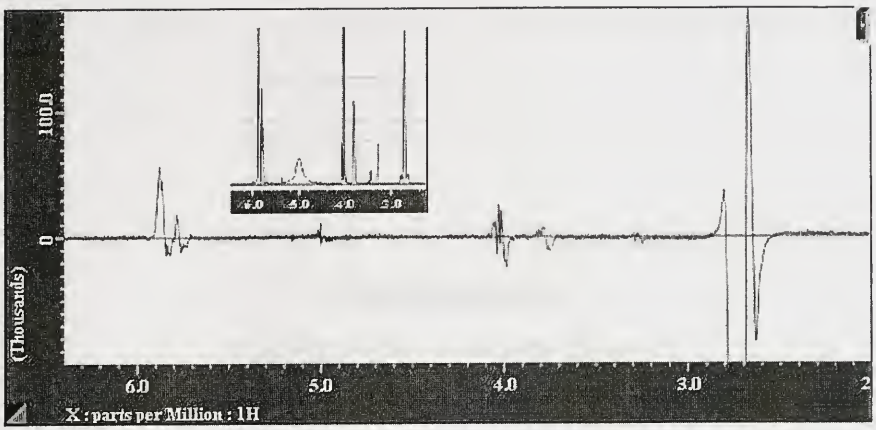


Figure 16: nOe of compound 37

With compound **37** in hand, 4-dimethylaminopyridine (DMAP) and 1,3-dicyclohexylcarbodiimide (DCC) were then employed to reform the lactone and subsequent rearrangement of the 1,4-diene to the 1,3-diene afforded 4,5-dihydro phthalide, compound **28**. The ^{1}H NMR of the crude material (94% yield, A-12) indicated the success of the ring closure, but also showed some unknown impurities. The sample was purified via column chromatography in a 1:1 hex/EtOAc to afford a white solid in 43% isolated yield.

The chemical shifts and splitting pattern of the signals for H-4 through H-7 were similar to that of **1**. Integration of peaks in ^{1}H NMR data (A-14) gave proper integration for the expected compound, with 8 hydrogens. Carbon-13 and the DEPT 135 NMR (A-15) of this compound showed the appropriate 8 carbons, 3 of which were quaternary carbons (C-1, C-3a, and C-7a), and 2 of which are methylenes (C-4 and C-5). Compound **28** was further confirmed via nOe, COSY (correlation spectroscopy), and HSQC (heteronuclear single quantum correlation) NMR (see A-16 – A-19). As seen in the nOe

(Figure 17) radiation of the peak assigned to H-7 affected the peaks assigned to H-6 and H-5.

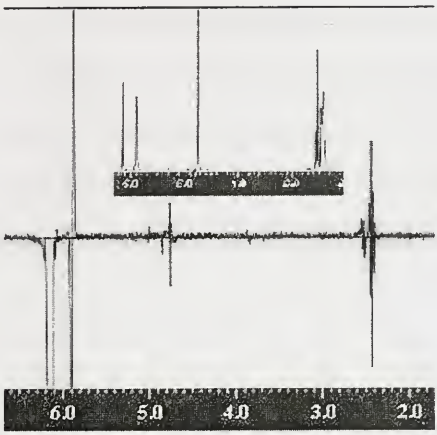


Figure 17: nOe of compound 28

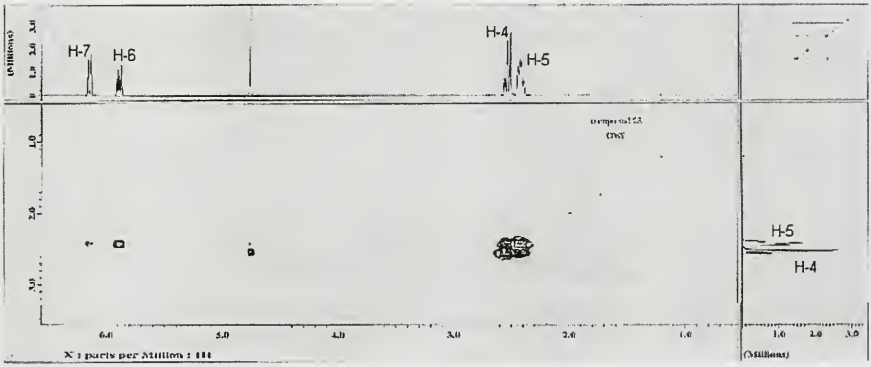


Figure 18: COSY of compound 28

The COSY (Figure 18) confirmed the labeling of all hydrogens. H-7 was adjacent to a doublet of triplets, which is the splitting pattern of H-6 in the synthesis of **1**. H-6 showed coupling with the vinyl signal furthest upfield, 2.38 – 2.45 ppm. The splitting for this hydrogen was a multiplet and according to the COSY was communicating with the

vinyl signal downfield at 2.49-2.56 ppm. This information confirmed that the multiplet at 2.36 ppm was H-5, and it was communicating with H-4, which was at 2.49 ppm. The peak thought to belong to H-3 was confirmed since it did not show any excess amount of interaction with other hydrogens. The HSQC (Figure 19) confirmed the hydrogen assignments. H-7 and H-6 were attached to methynes (C-6 128.68; C-7 116.63 ppm), while H-4 and H-5 were attached to methylenes (C-4 21.15; C-5 22.19 ppm). Compound **28** is thoroughly characterized here due to the original reference 22 providing inadequate spectra.

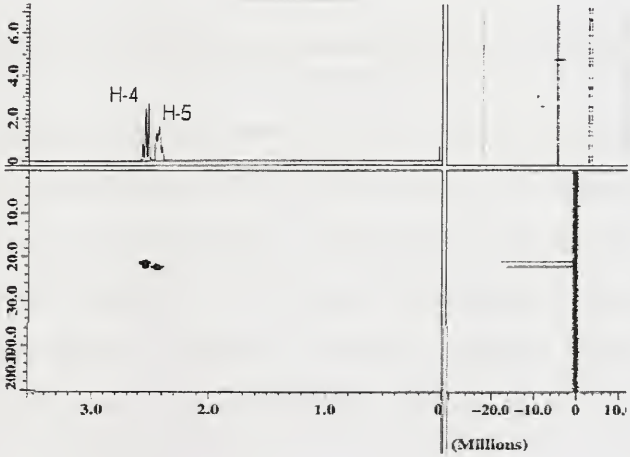


Figure 19: HSQC of compound 28

Upon the successful synthesis and isolation of **28**, step 2 of Synthetic Scheme 1 (Scheme 15) was attempted. Due to time constraints, purification of the expectant compound **21** was not possible, but ^{1}H NMR data of the crude product (A-21) indicates a successful reaction. The aromatic peaks of the benzyl ring and H-7, H-6 peaks appear at the same frequency, and the aldehyde peak is significantly less in frequency than the

aromatic peaks indicating that the aromatic signals do not belong to the starting material. The TLC of the reaction (Figure 20) indicates a variety of products, which can be possible diastereomers of compounds **21** and **34**. The TLC also indicates that the products can be successfully isolated due to the large difference in R_f values.

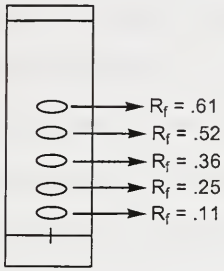
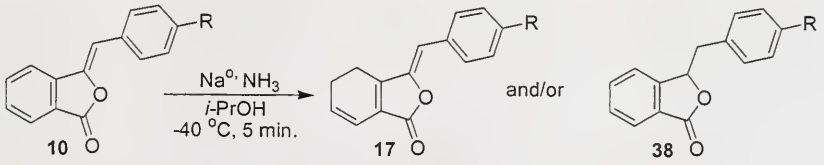


Figure 20: TLC of crude material from the addition of the aromatic alcohol moiety to compound 28

Synthetic Scheme 2 addressed the problem of decomposition of **20** by performing the Birch on compound **10a**. Previous Birch reductions were performed on the alcohol derivatives to avoid the possibility of reducing the π bond between C-3 and C-8, compound **38** (Scheme 17). Due to its benzylic location between two aryl rings, the C-3 and C-8 bond may be susceptible to reduction under Birch conditions. However, literature research did not indicate the approach to be unsuccessful.

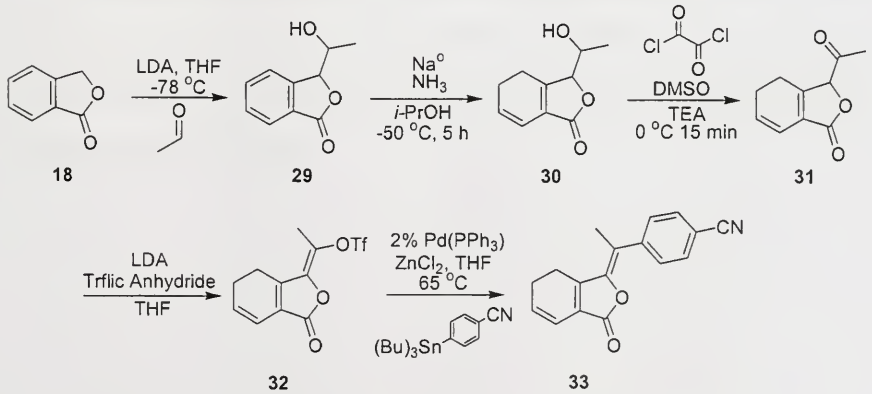


Scheme 17: Synthetic Scheme 2 with proposed conditions

Initial analysis of ^1H and ^{13}C NMR data was inconclusive. ^1H NMR data indicated the possibility of compound **17**, but the DEPT proved otherwise, indicating 3

methylenes in the compound. To further investigate and identify the unknown compound the reaction was repeated exactly. Proton NMRs (A-22) indicated that the same compound was synthesized in reaction 2 as reaction 1, however, ^{13}C and DEPT NMR, (A-23 and A-24) proved otherwise. Carbon-13 NMR for reaction 1 indicates the presence of 13 carbons, while reaction 2 indicated the presence of 12 carbons. Reaction 1 had a carbon at 45.72 ppm, which was not seen in the ^{13}C of reaction 2, and reaction 2 indicated a carbon at 164.65 ppm, which was not seen in reaction 1. DEPT NMR of both reactions also indicated contrasting information. Reaction 1 indicated three methylenes, while the compound for reaction 2 indicated 4 methylenes. The compounds formed in both reactions did not give conclusive data on the possible structure of either molecule. It is possible the extraneous peaks were due to contaminants. Synthetic Scheme 2 was discontinued due to time constraints and a clear indication that compound **17** was not the synthesized compound.

Synthetic Scheme 3 was a novel approach that addressed the problems of formation of compound **20** encountered during the Birch (Scheme 18).



Scheme 18: Synthetic Scheme 3 with proposed initial conditions

Conditions for the addition of the ethyl alcohol moeity, compound **29**, and reduction of the phthalide ring to afford **30** were followed directly from the synthesis of **1**,[11] but in this synthesis acetaldehyde was used instead of butylaldehyde. The first two steps of Synthetic Scheme 3 are expected to work due to their similarity to the synthesis of **1**. The reduction of **29** to afford **30** is expected to be successful and not result in the decomposition of **29** for the same reasons explained previously in Scheme 10. Following the synthesis of compound **30** is the Swern oxidation of the alcohol group to form a ketone,[23] **31**. Formation of the enolate, followed by trapping with Tf_2O is expected afford compound **32**. An uncertainty involving the triflation of compound **30** is whether the product obtained would be the kinetic or thermodynamic product, Figure 21.

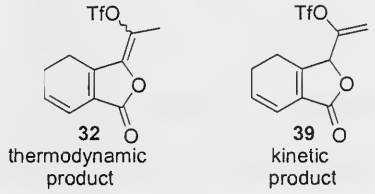


Figure 21: Kinetic vs. thermodynamic product

A kinetic controlled product is determined by relative rates for the two or more acidic hydrogens (Figure 22).[19] If an equilibrium is established between those two products, A and B, then the stability of the enolate is determined by the thermodynamic controlled product (Figure 23).[19]

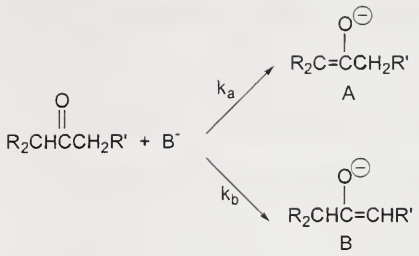


Figure 22: Kinetic control of enolate formation

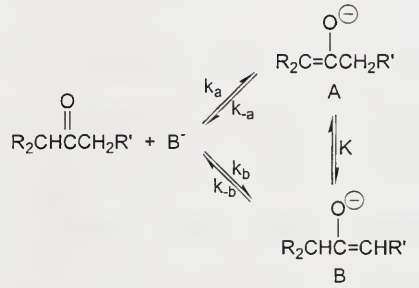


Figure 23: Thermodynamic control of enolate formation

Kinetic or thermodynamic control can be obtained through the adjustment of the conditions to obtain the enolate.[19] In the case of kinetic control, the ideal conditions require that the formation of an enolate be under rapid deprotonation, quantitative, and irreversible.[19] In order to achieve these ideals, a strong base such as LDA or hexamethyldisilazane (HMDS) is used in an aprotic solvent, with the absence of excess ketone.[19] Lithium is used over sodium or potassium because it maintains a tighter coordination at the oxygen and reduces the rate of proton exchange.[19] Aprotic solvents and the absence of excess ketone also reduce the chance of proton exchange and the formation of an equilibrium which would result in thermodynamic control over kinetic control.[19] Kinetic control usually favors the less substituted enolate for steric purposes, while thermodynamic control forms an equilibrium between the most substituted

enolates.[19] The stability of the carbon-carbon double bond increases with increased substitution and this effect leads to greater stability of the more substituted enolate.[19] The diene in compound **32** is tetrasubstituted versus the diene in compound **39**, which is disubstituted. Since **32** is the more substituated diene and has a more stable enolate than compound **39**, it is safe to assume that it is the product of thermodynamic control. Conditions to obtain **32** will be altered accordingly to obtain the thermodynamic compound.

After compound **32** is acquired, removal of the triflate and addition of the aromatic moiety via palladium-catalyzed coupling[24] is expected to provide compound **33**. Compound **33** differs from **17** in that the hydrogen at C-8 is now a methyl group. Although the methyl group makes C-8 slightly sterically hindered compared to having a hydrogen in that position, the sterics are not expected to hinder the bioactivity of the compound. C-8 in compound **33** will still be destabilized by the EWG on the aromatic ring. Compound **33** also maintains conjugation with the 1,6-system, therefore it essentially preserves all of the characteristics that were sought in the synthesis of **17**.

The ^{1}H NMR for the synthesis of **29** indicated the presence of **29**. Purification of the crude material via column chromatography in a 1:3 hex/EtOAc eluent system afforded **29** in a 38% isolated yield. The expected change in ^{1}H NMR was the addition of the alcohol and ethyl peaks as well as the peak for H-3 changing from a singlet to a doublet, 5.31 ppm (A-29). Aromatic signals were maintained, and the presence of the alcohol peak at 3.52 ppm, methyl peak, a doublet at 1.15 – 1.20 ppm, and a methyne peak at 3.99 ppm confirmed the addition of the ethyl alcohol moiety by integrating to 1, 3, and 1 hydrogen(s), respectively. The ^{1}H NMR also indicated the presence of both

diastereomers. An nOe (A-28, Figure 24) irradiating H-8 resulted in the enhancement of peaks H-3 and H-9.

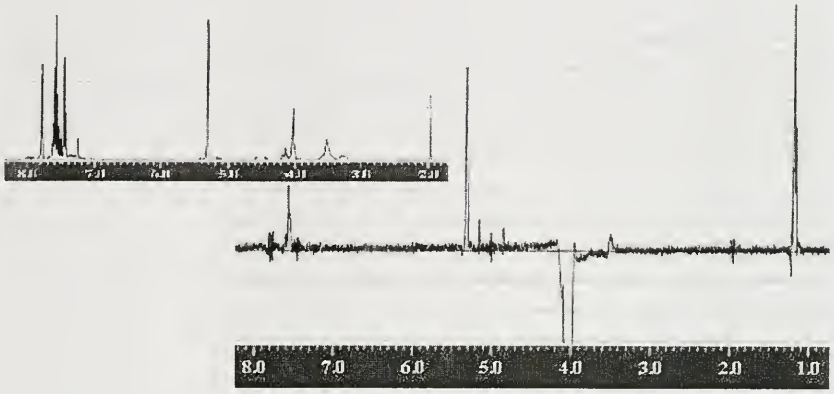


Figure 24: nOe of compound 29

The ^{13}C NMR (A-27) of this compound confirmed the presence of 9 carbons and the DEPT 135 NMR further confirmed the presence of 7 methynes and methyls total. The disappearance of two signals confirmed the quaternary carbons, C-3a and C-7a. The COSY (A-29, Figure 25) of **29** also indicated interaction between the peaks assigned to H-3 and H-8, and H-8 and H-9.

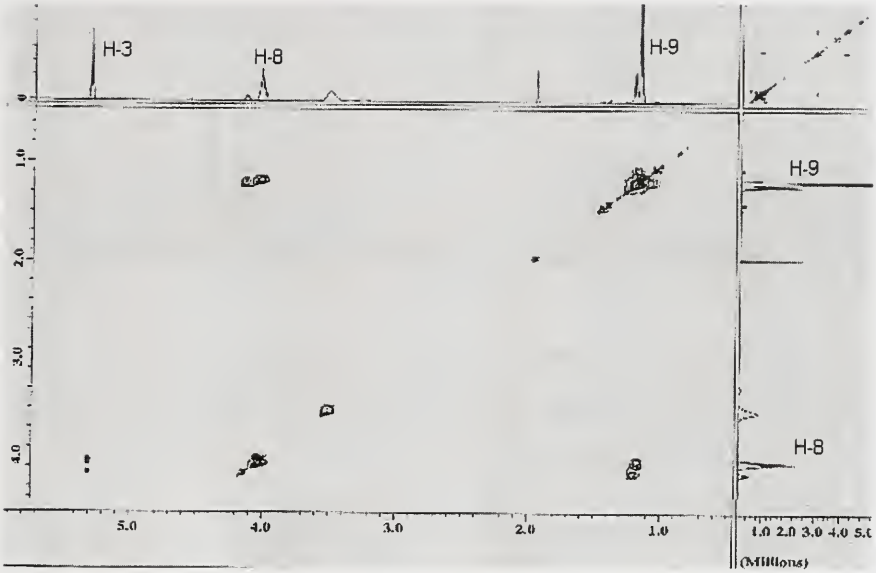


Figure 25: COSY of compound 29

Further analysis of the HSQC (A-30) helped to assign the protons to their carbons. It was clearly indicated which carbons belonged to H-3 (C-3, 84.56 ppm), H-8 (C-8, 68.90 ppm), and H-9 (18.32 ppm) because of an absence of noise in these signals. A closer look at the aromatic region (Figure 26) allowed for the assignment of the aromatic hydrogens to their respective carbons.

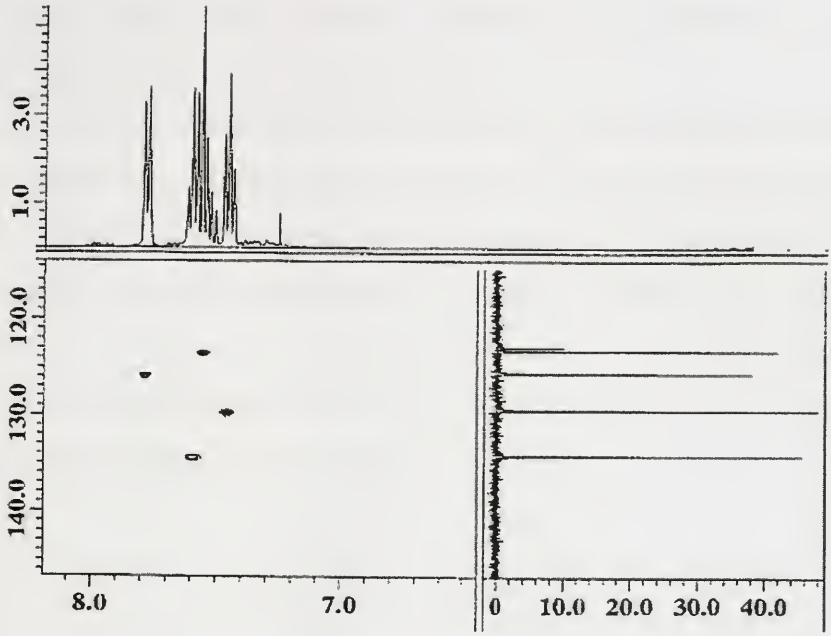


Figure 26: HSQC of the aromatic region in compound 29

The reduction of compound **29** proved to be partially successful, giving both starting material and product, which were inseparable by column chromatography. As seen in the ^{1}H NMR of the crude material (A-32) the peaks at approximately 6.2 ppm and 6.0 ppm indicated the possibility of the reduced product, **30**. Column chromatography in a 1:2 acetone/pet. ether eluent system was used in an attempt to isolate **30**. As seen in the ^{1}H NMR, compound **30** was not isolated (A-33). The fraction nb-viii-34-13 was supposed to contain only the product, corresponding to the spot with an R_f value of 0.36, while for fraction nb-viii-34-14 the indicated spot and a little bit of the spot underneath were collected. In the fraction corresponding to nb-viii-34-13 there are several impurities including starting material in the sample. Preparatory plates were performed on the crude

reduced material, however separation of the product once again proved to be unsuccessful despite single rows being collected.

Initially, it was thought that the Birch reduction was unsuccessful due to the vast number of the products being produced. Since the Birch reductions were unsuccessful on compounds **18**, **10**, and **29**, the problem was thought to lie somewhere else other than the compounds being reduced, and the synthesis of **1** was rerun to determine if this was the case. The reduction of 3-hydroxybutylphthalide, **40**, to afford 4,5-dihydro-3-hydroxybutylphthalide, **41** (Figure 27) while still successful did not yield as much product as reported previously, (1:7 **40**:**41** vs. 1:14 **40**:**41**).[10]

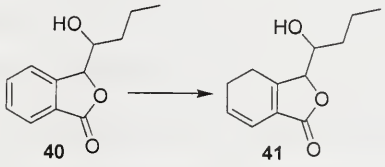


Figure 27: Birch reduction of 40 to provide 41

Purification of the compound once again proved to be ineffective during isolation of **41**. Because all solvents used were distilled prior to use, ammonia was thought to be the problem. Distillation of the ammonia prior to used did not provide an explanation but instead resulted in a decrease in yield of **41**, 1:4 **40**:**41**. The cause of the poor yielding Birch reductions is still unknown, and due to time constraints could not be further investigated.

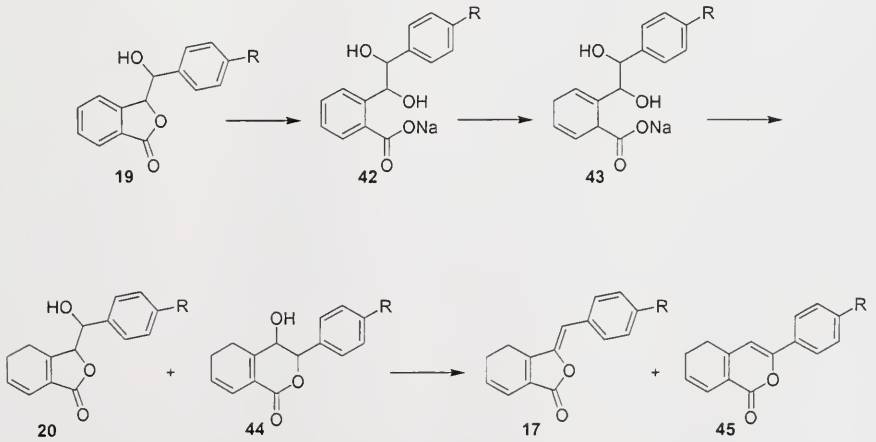
~ Conclusion ~

The proposed Synthetic Schemes 1, 2, and 3 did not successfully afford the target compound **17**. The etiology of the low-yielding Birch reductions is unknown, and due to time constraints a full investigation into the cause could not be initiated and a definitive explanation cannot be provided. The discovery of a key reference did, however provide alternate synthetic methods that could be applied to Synthetic Schemes 1 and 3. The key step found in reference 22 allowed for the successful synthesis of compound **28** and possibly compound **20** from Synthetic Scheme 1, and if further pursued could result in the attainment of compound **17**. If pursued further Synthetic Scheme 3 could also result in the successful synthesis of **33**. This key reference provided new routes for the synthesis of **17** as well other potentially bioactive compounds. Although the target compound was not successfully synthesized, the discovery of various other methods provides optimism that completion of the project may be attainable by other researchers.

~ Future Research ~

The discovery of the methodology provided in reference 22 has provided alternate approaches to Synthetic Scheme 1 (previously stated) as well as Synthetic Scheme 3. As shown earlier in Scheme 16, reduction of the aromatic ring of phthalide (with the lactone open as the sodium carboxylate) proved to be effective in providing **28**. The discovery of this synthesis also provides a new approach to Synthetic Scheme 3. Theoretically, with **28** in hand, the ethyl moiety could be added to the phthalide ring to provide **30**, followed by the last 3 steps to obtain compound **33**.

Another approach to obtain target compound **17** is a modification of Scheme 7 to provide the synthesis shown in Scheme 19. It is plausible to obtain the diol acetate and run Birch conditions to afford the dihydro compound, and then ring closure to give either the γ lactone, **17**, or the δ lactone, **45**. Attainment of compound **45** would not be a setback because it maintains the 1,6 system and, if bioactive, could result in a new framework.



Scheme 19: A possible future synthetic scheme for the target compound 17

Although compound 17 was not acquired through these investigative efforts, the possibility of obtaining this product has not diminished. On the contrary, the results obtained from these studies have provided several new viable methods.

General Experimental – All reactions were run in oven-dried glassware under an argon atmosphere. Final solutions were dried over Na_2SO_4 prior to concentration. THF was distilled over Na/benzophenone and CH_2Cl_2 was distilled over CaH_2. All chemicals were purchased from Aldrich Chemical Company and purged with argon after every use. All solvents were distilled prior to use. Phthalide was recrystallized from H_2O and dried under high-vacuum for 24 h. TLC were performed on precoated glass silica gel plates. NMR spectra were obtained on a JEOL ECX400 spectrometer. All chemical shifts are reported in ppm and J values in Hertz.

Synthetic Scheme 1

2-(hydroxymethyl)benzoic acid (36) – To a stirred mixture of phthalide (2.68 g, 20 mmol) and MeOH (1 M solution) was added 2 M NaOH (20 mL, 40 mmol). The mixture was refluxed for 1h, cooled to rt and the solvent was removed *in vacuo*.[22] ^{1}H NMR – δ 7.73 (d, J = 7.33, 1H), 7.32 (d, J = 3.66, 2H), 7.24-7.29 (m, 1H), 4.67 (s, 2H).

2-(hydroxymethyl)cyclohexa-2,5-dienecarboxylic acid (37) – To a stirred solution of **36** (3.48 g, 20 mmol) and MeOH (6.88 mL, 170 mmol) was added NH_3 (*ca.* 43 mL), followed by Na^o (1.6 g, 71.6 mmol) at –78 °C. The resultant solution changed to the expected blue upon addition of Na^o, but reverted to white after 2-3 minutes. The rbf was removed from the cold bath and the NH_3 allowed to reflux (with the cold finger at – 78 °C) for 1 h, after which MeOH (4 mL) and H_2O (30 mL) were added. The mixture was stirred for 3 h, diluted with EtOAc (30 mL) and transferred to a separatory funnel. The aqueous layer was acidified with 3 M HCl until pH ~1, layers partitioned, and the organic layer was washed with saturated brine (1 x 20 mL), dried, and concentrated *in vacuo*.

The product was recrystallized in 2:1 Hex/EtOAc to afford a white solid at a 21% yield.[22] ^{1}H NMR - δ 5.85 – 5.88 (m, 2H), 5.77 – 5.80 (m, 1H), 5.00 (s, 1H), 4.04 (quat, J = 13.28, 6.41, 2H), 3.80 (quat, J = 6.87, 4.12, 6.14, 1H), 2.73 (m, 2H).

4,5-dihydrophthalide (28) – To a stirred solution of **37** (0.36 g, 2.06 mmol) and CH_2Cl_2 (0.7 M solution) was added DCC (0.241 g, 2.41 mmol) and DMAP (0.013 g, 0.010 mmol). The solution was allowed to stir at rt for 2 h, and then filtered through a pad of Celite using $CHCl_3$ as a rinse. Filtrates were concentrated *in vacuo* and chromatographed with a 1:1 Hexanes/EtOAc mixture to afford a white powder at a 43% yield.[22] ^{1}H NMR – δ 6.14 (dt, J = 1.83, 2.29, 1H), 5.89 (dt, J = 4.12, 0.92, 4.58, 1H), 4.75 (s, 2H), 2.54 (m, 2H), 2.42 (m, 2H).

Synthetic Scheme 3

3-(1-hydroxyethyl)phthalide (29) – To a stirred solution of THF (9.33 mL) and diisopropylamine (DIPA) (1.16 mL, 8.21 mmol) at –78 °C was added *n*-butyllithium (1.35 M, 8.21 mmol). A solution phthalide (1 g, 7.46 mmol) in THF (18.65 mL) was dripped into the reaction flask over a 30 min period to afford an orange slurry. The reaction mixture was stirred for 10 min., then a 1:1 solution of acetaldehyde/THF (0.92 mL) was added resulting in the dissipation of the orange slurry. The mixture was stirred for 15 min., quenched with ice chunks (*ca.* 6 g) and removed from the – 78 °C bath. The THF was removed *in vacuo*, and the solution transferred to a separatory funnel and diluted with EtOAc (50 mL). 1.5 M HCl was added until the pH of the aqueous layer was ~3. The aq. layer was rinsed with EtOAc (2 x 50 mL). The organic layer dried and concentrated *in vacuo*. The crude material was chromatographed with a 1:3 Hex/EtOAc solution to afford an off-white solid, 38% yield.[11] ^{1}H NMR – δ 7.78 (d, J = 7.79, 1H),

7.56 (m, 2H), 7.45 (t, J = 7.33, 1H), 5.31 (t, J = 4.58, 1H), 4.04 (quin, J = 5.95, 5.04, 6.41, 6.87, 1H), 3.52 (s, 1H), 1.18 (d, J = 6.41, 3H).

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Appendix

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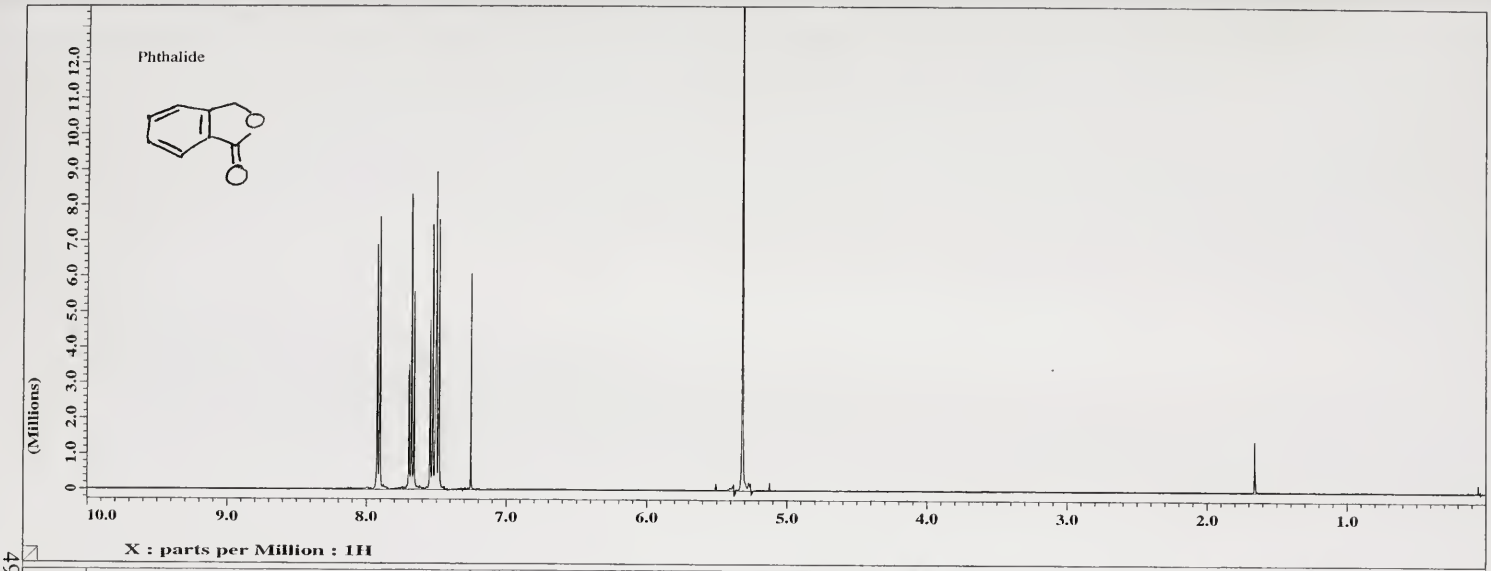
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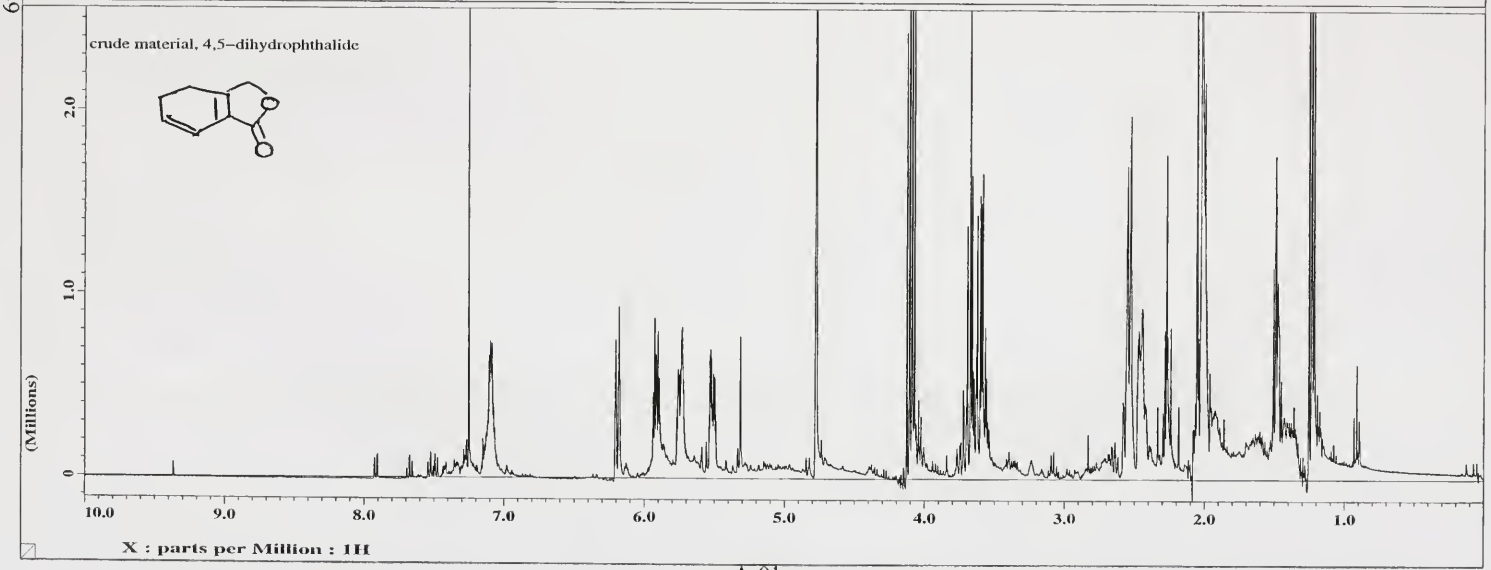
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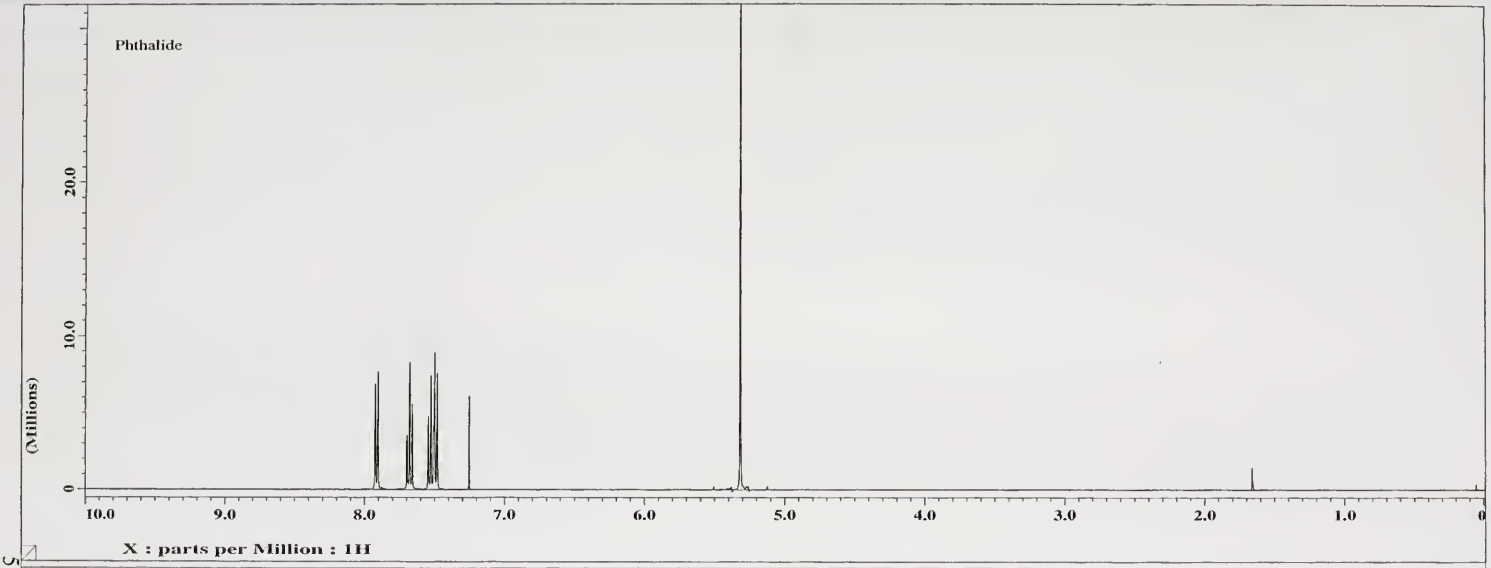
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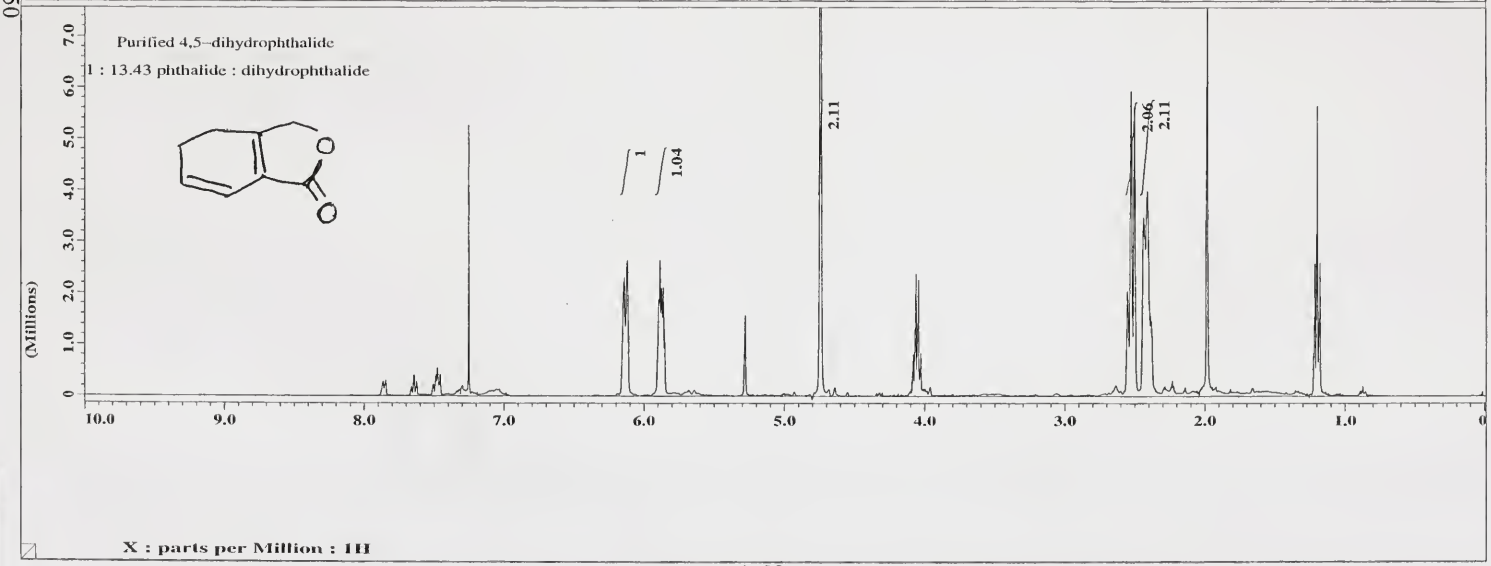
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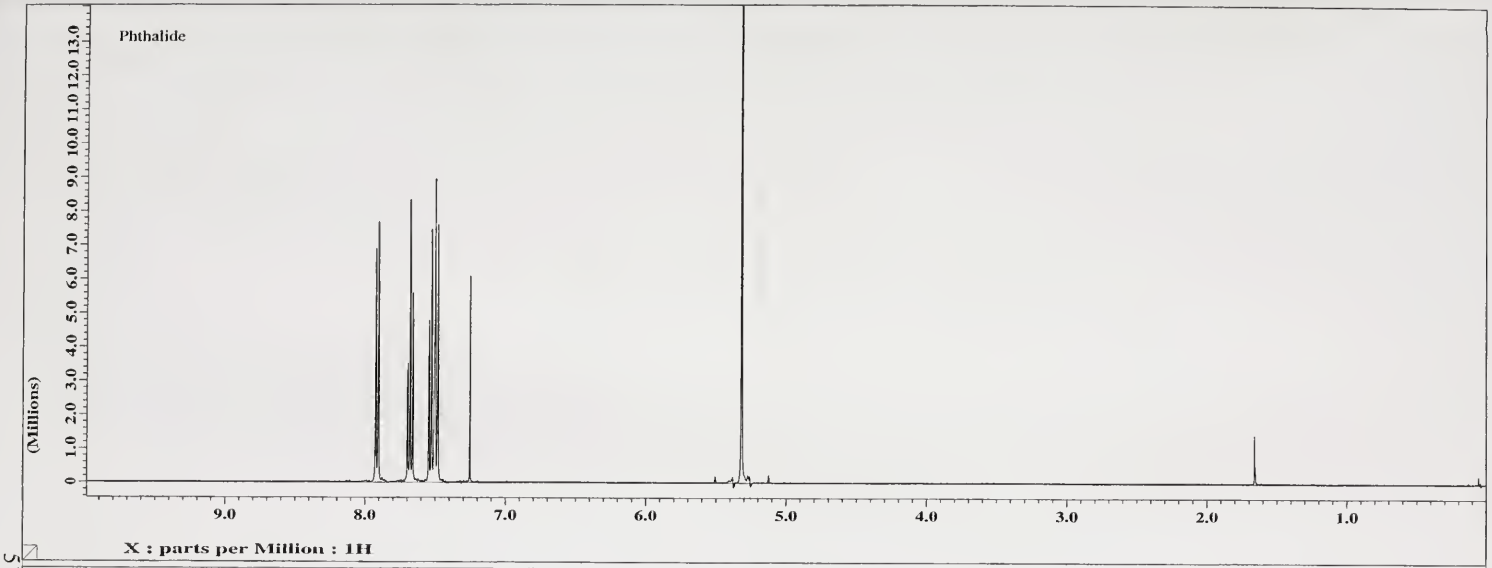
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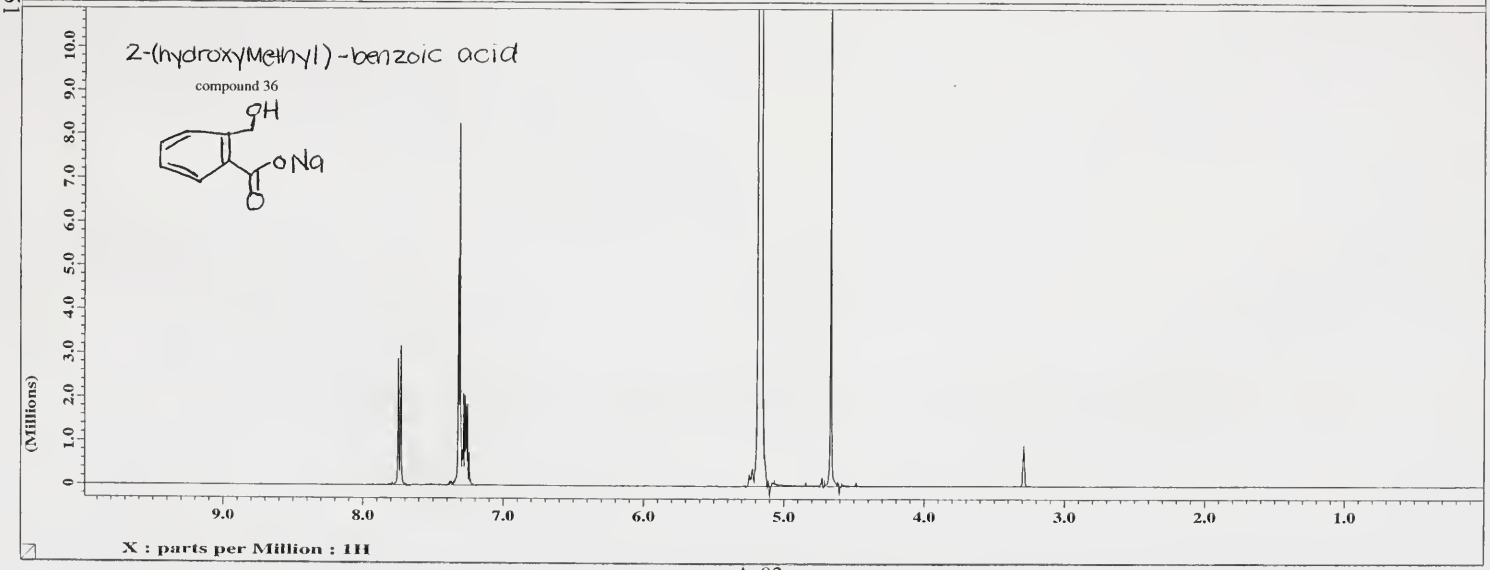
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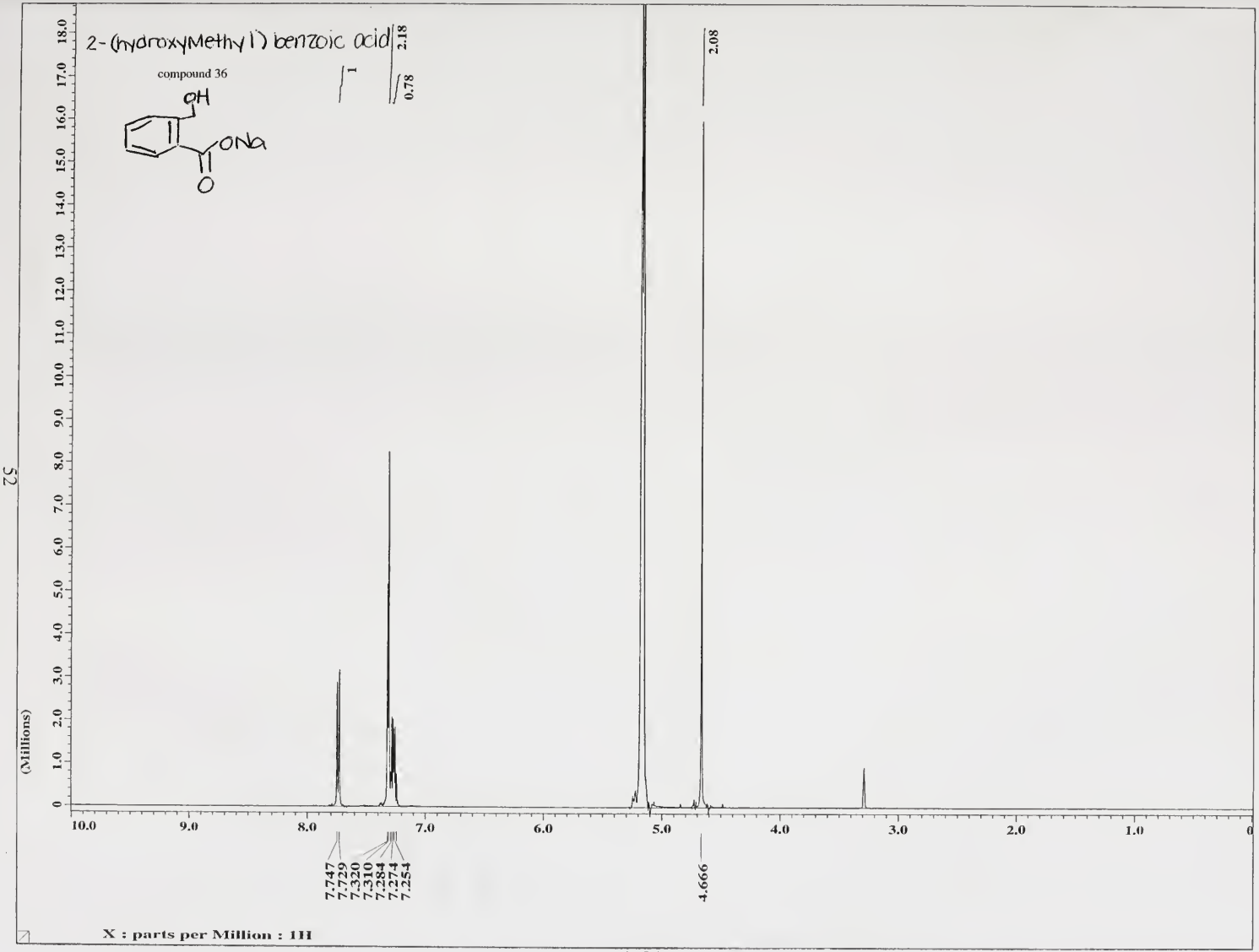
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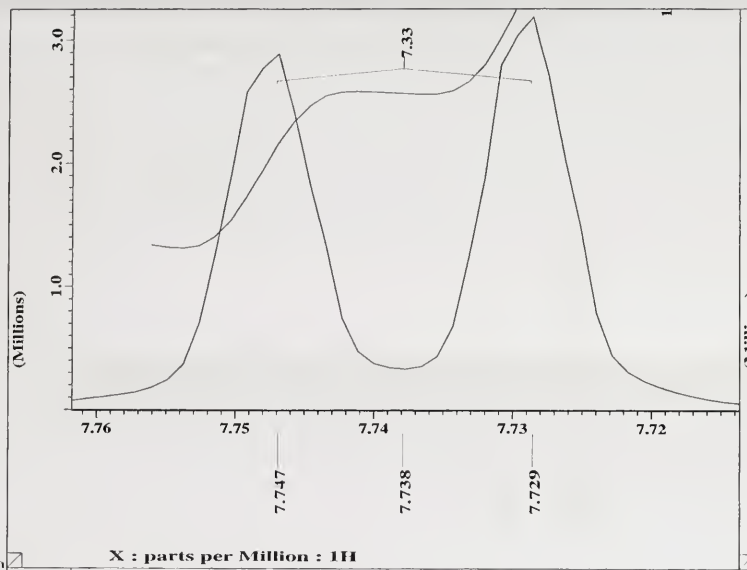
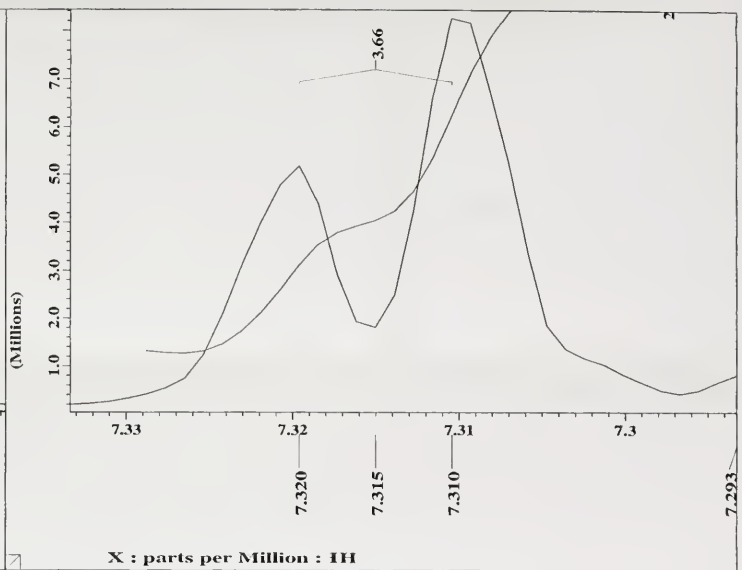
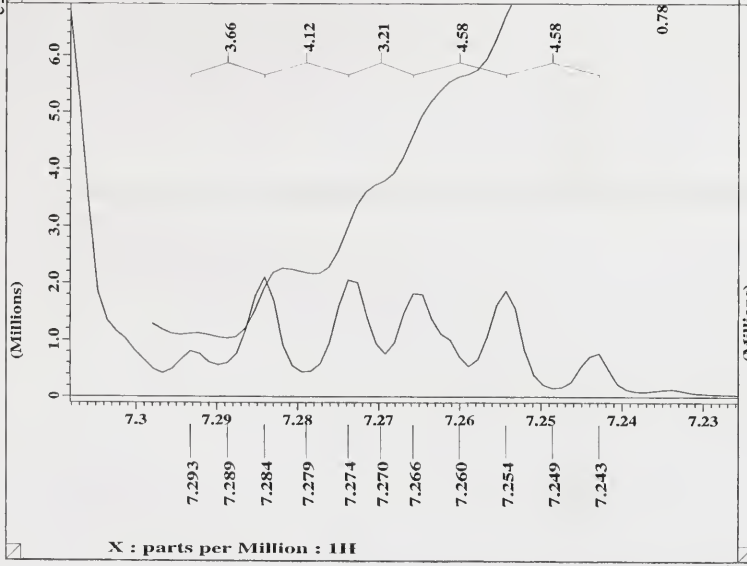
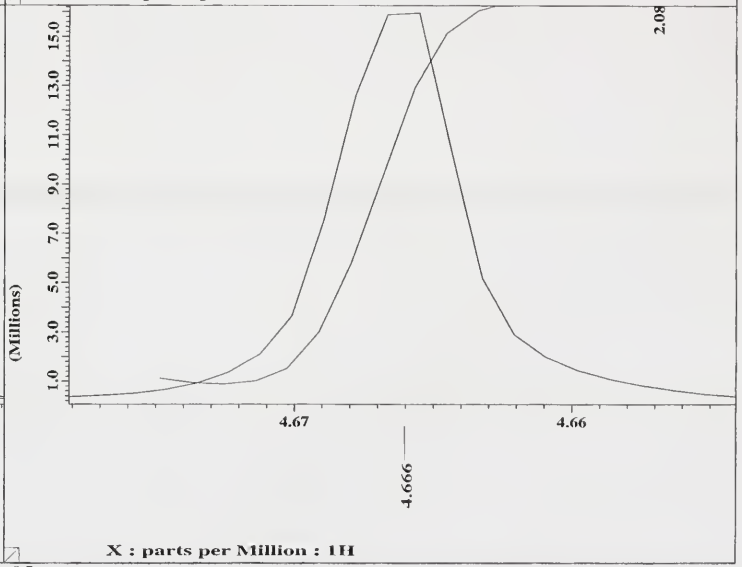
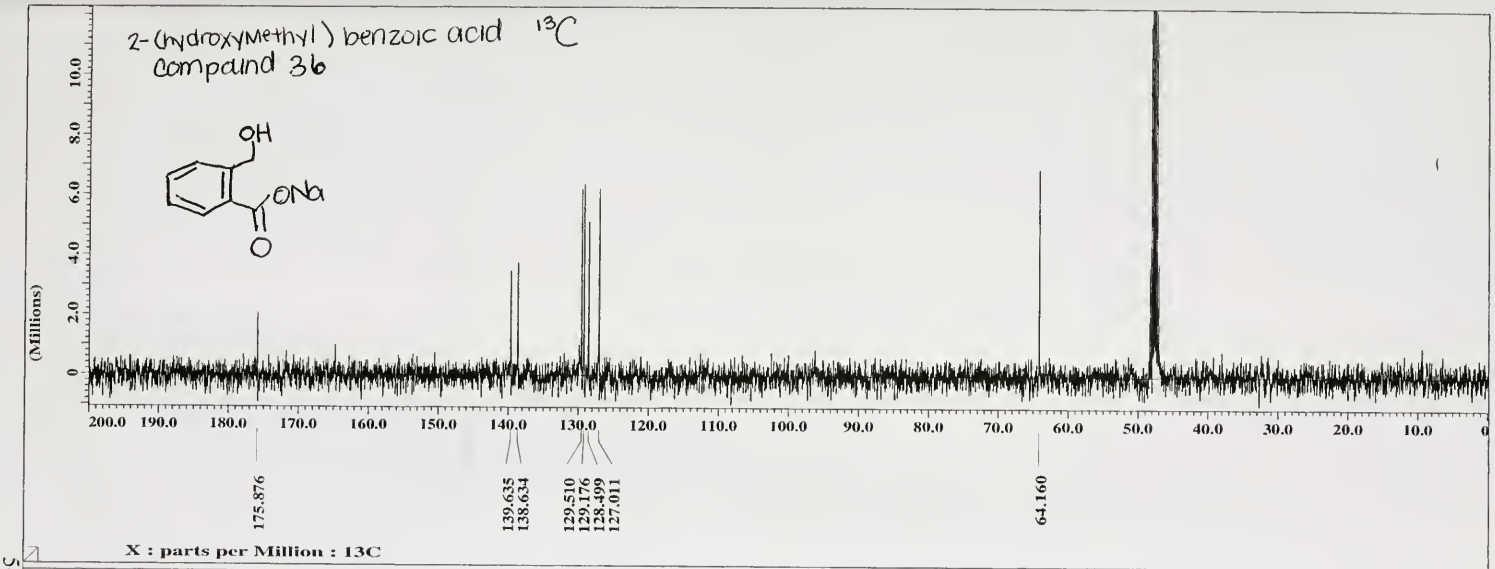
4.666
X : parts per Million : 1H

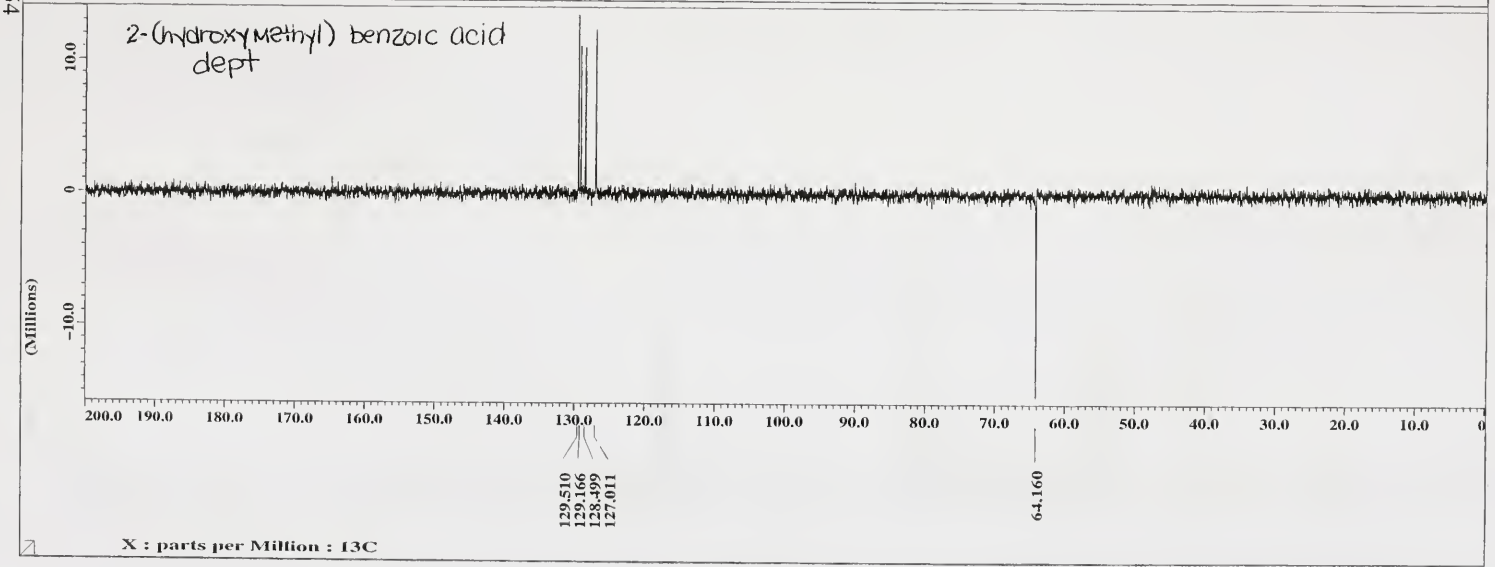

7.33
(Millions)
7.76
7.75
7.74
7.73
7.72
7.747
7.738
7.729
X : parts per Million : 1H

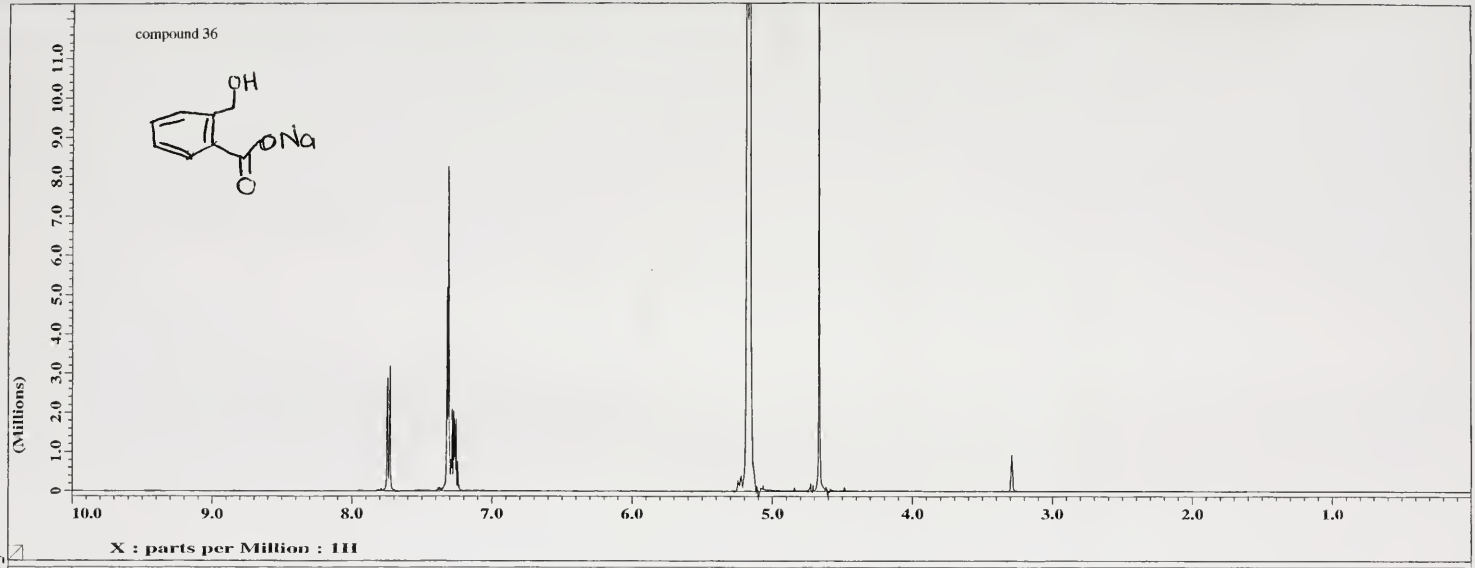

3.66
(Millions)
7.33
7.32
7.31
7.3
7.320
7.315
7.310
7.293
X : parts per Million : 1H

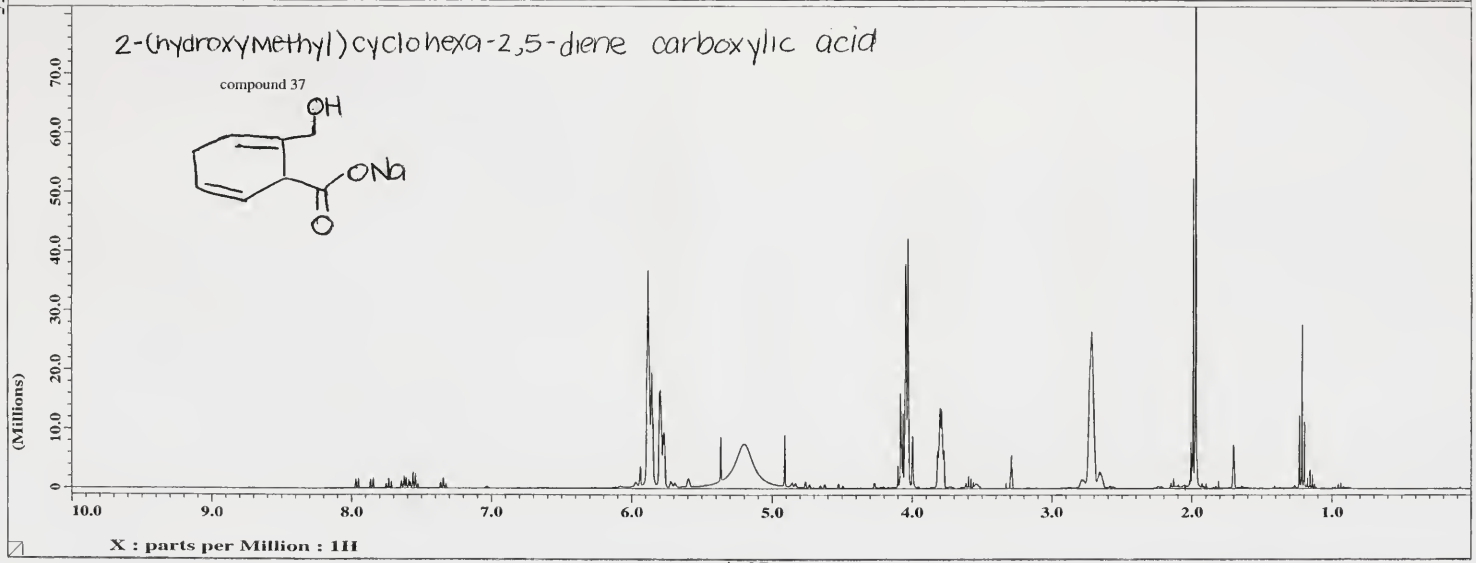

3.66
4.12
3.21
4.58
4.58
0.78
(Millions)
7.3
7.29
7.28
7.27
7.26
7.25
7.24
7.23
7.293
7.289
7.284
7.279
7.274
7.270
7.266
7.260
7.254
7.249
7.243
X : parts per Million : 1H

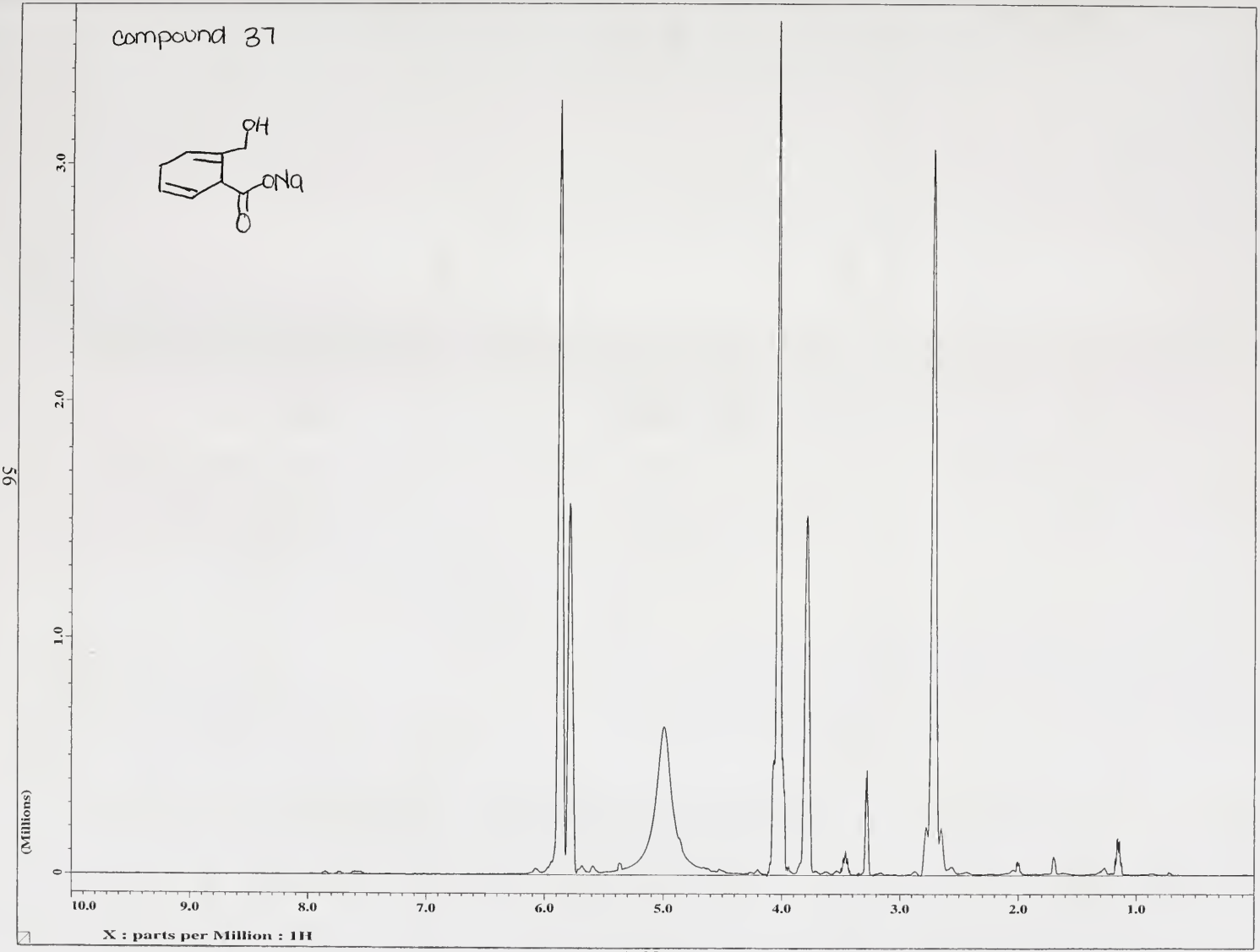

2.08
(Millions)
4.67
4.66
4.666
X : parts per Million : 1H

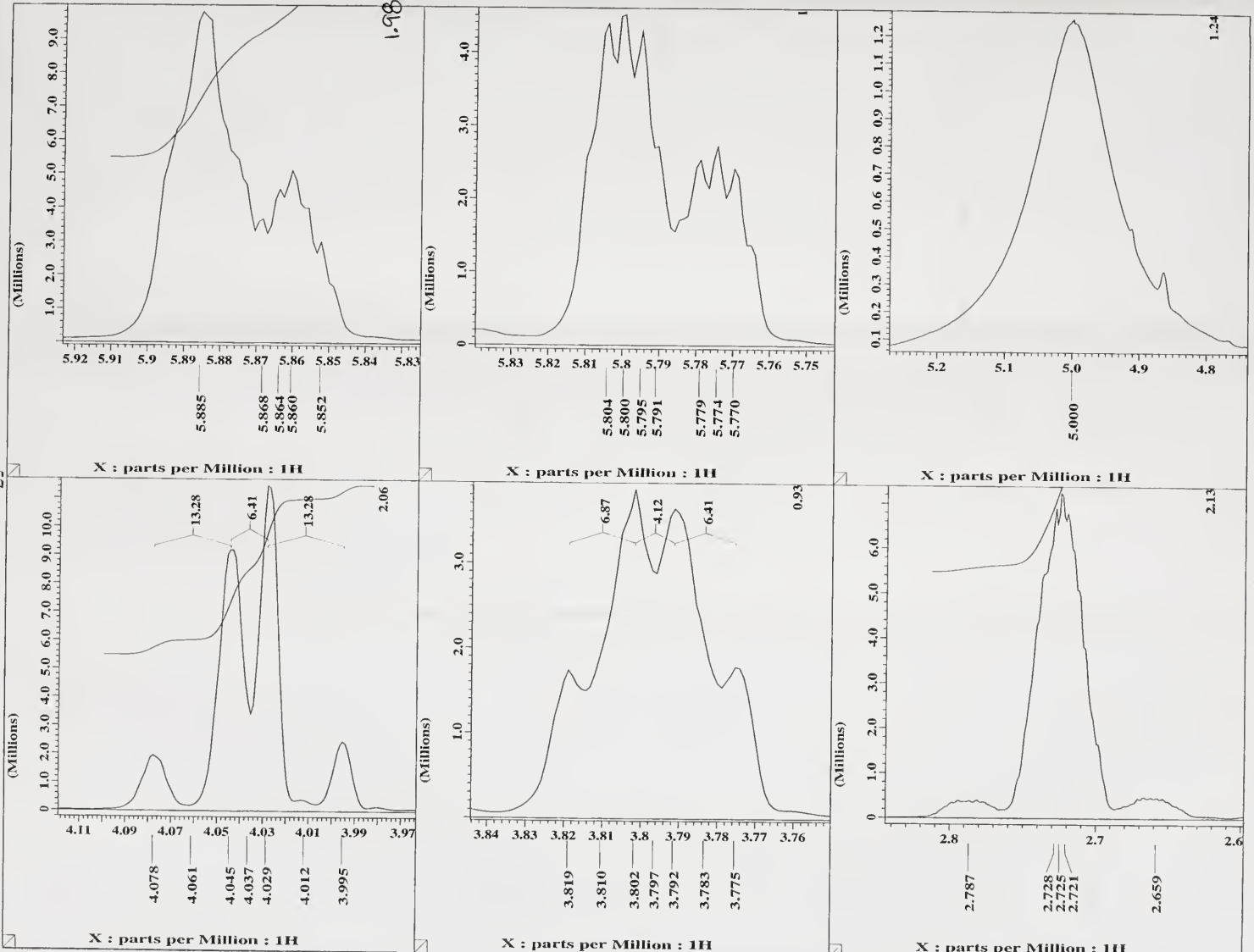

2-(hydroxymethyl) benzoic acid ^{13}C
compound 36
OH
ONa
O
(Millions)
10.0
8.0
6.0
4.0
2.0
0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
175.876
139.635
138.634
129.510
129.176
128.499
127.011
64.160
X : parts per Million : 13C

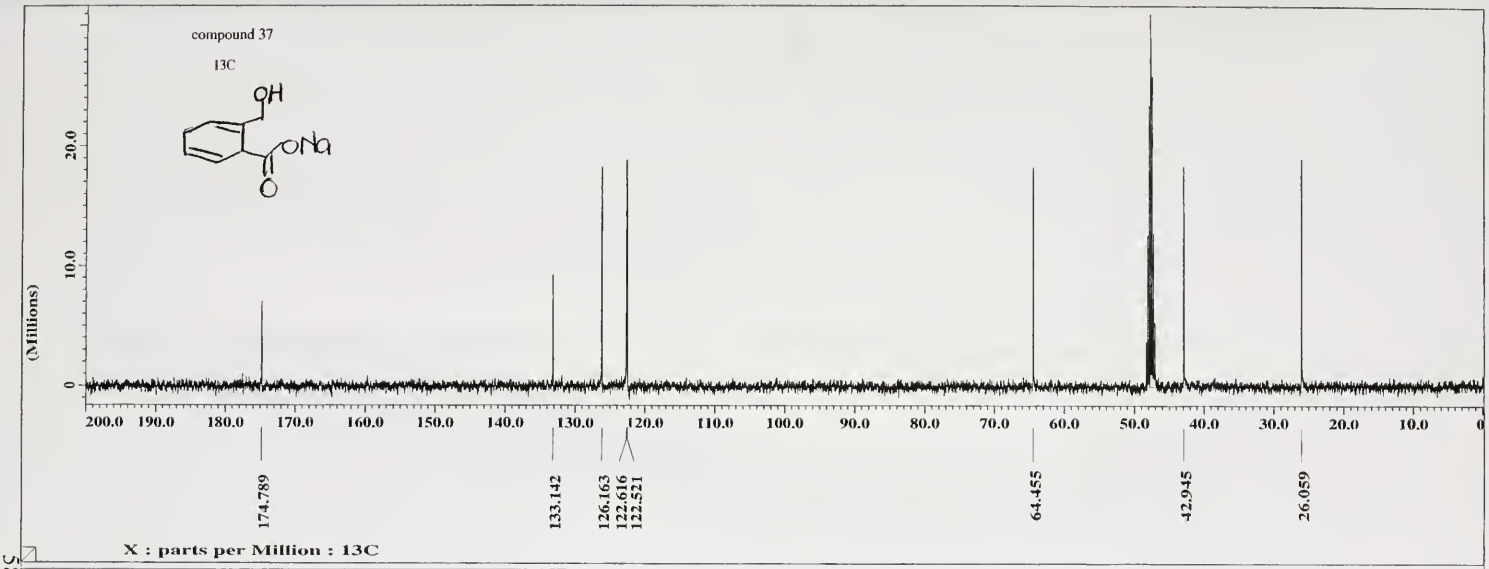

2-(hydroxymethyl) benzoic acid
dept
(Millions)
10.0
0
-10.0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
129.510
129.166
128.499
127.011
64.160
X : parts per Million : 13C

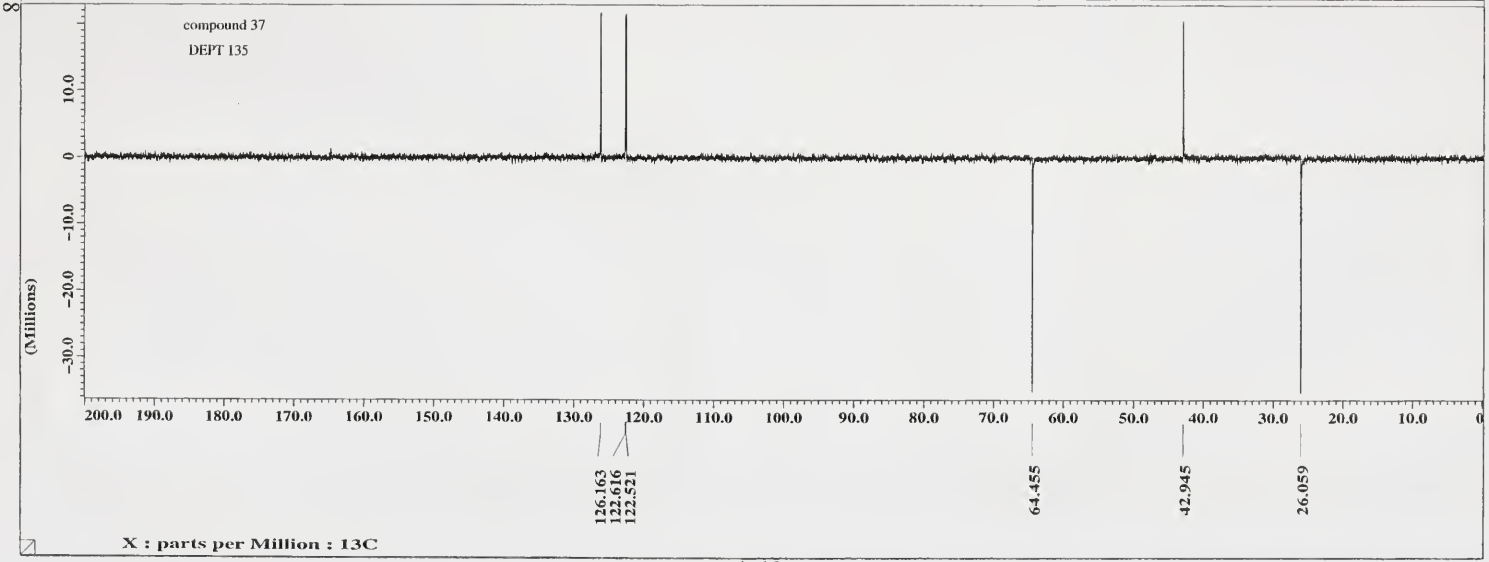

compound 36
OH
ONa
O
(Millions)
0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H

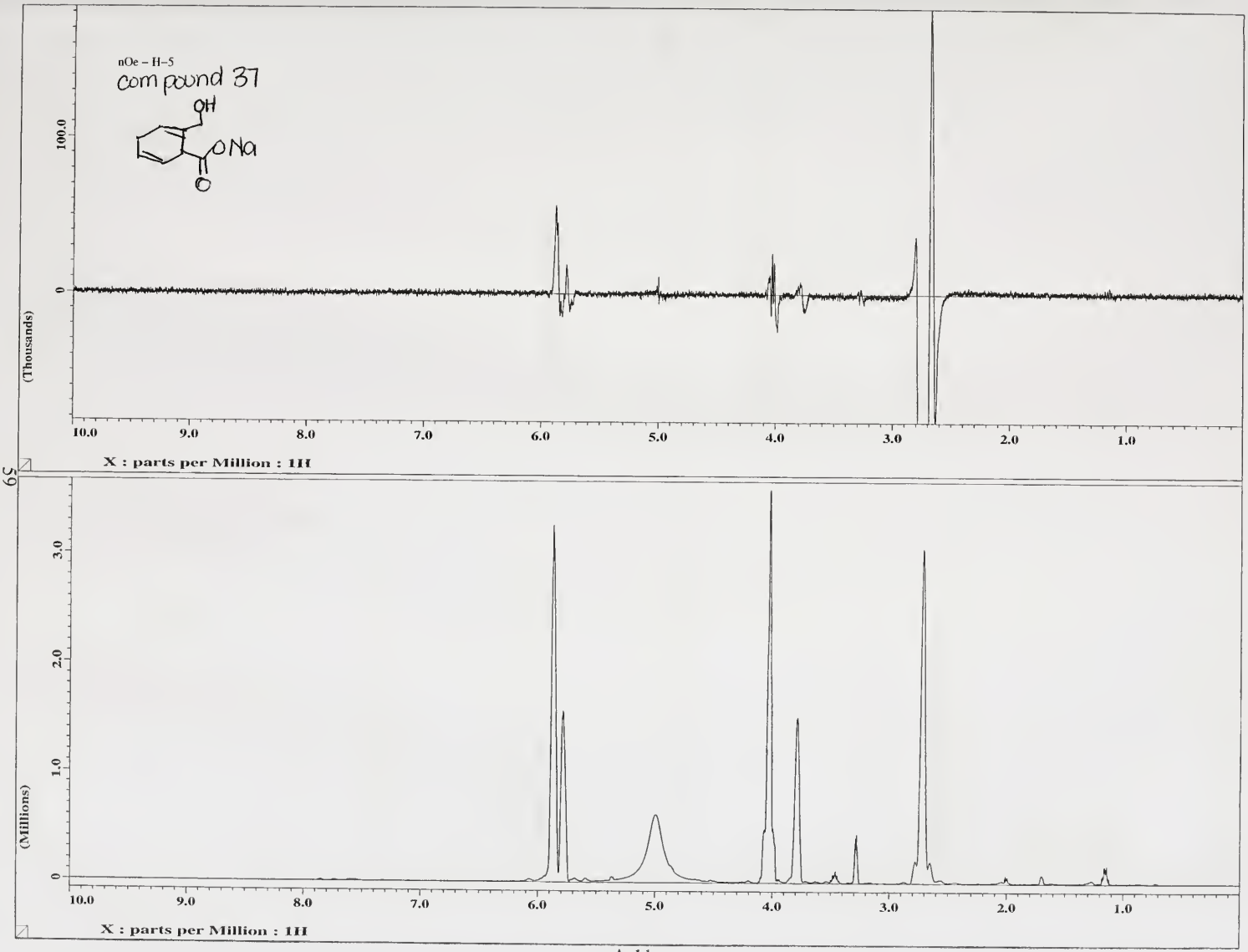

2-(hydroxymethyl)cyclohexa-2,5-diene carboxylic acid
compound 37
OH
ONa
O
(Millions)
0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H

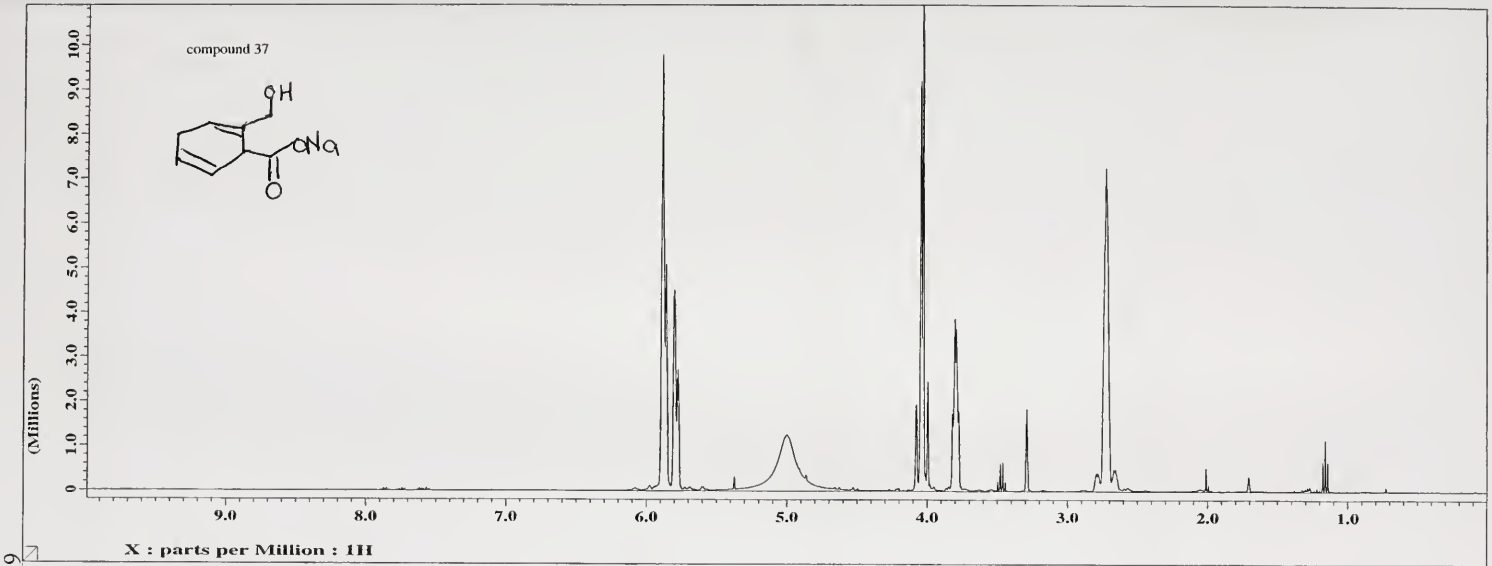

compound 37
OH
ONa
O
3.0
2.0
1.0
0
(Millions)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H


(Millions)
5.885
5.868
5.864
5.860
5.852
X : parts per Million : 1H
5.804
5.800
5.795
5.791
5.779
5.774
5.770
X : parts per Million : 1H
5.000
X : parts per Million : 1H
13.28
6.41
13.28
2.06
4.078
4.061
4.045
4.037
4.029
4.012
3.995
X : parts per Million : 1H
6.87
4.12
6.41
0.93
3.819
3.810
3.802
3.797
3.792
3.783
3.775
X : parts per Million : 1H
2.13
2.787
2.728
2.725
2.721
2.659
X : parts per Million : 1H

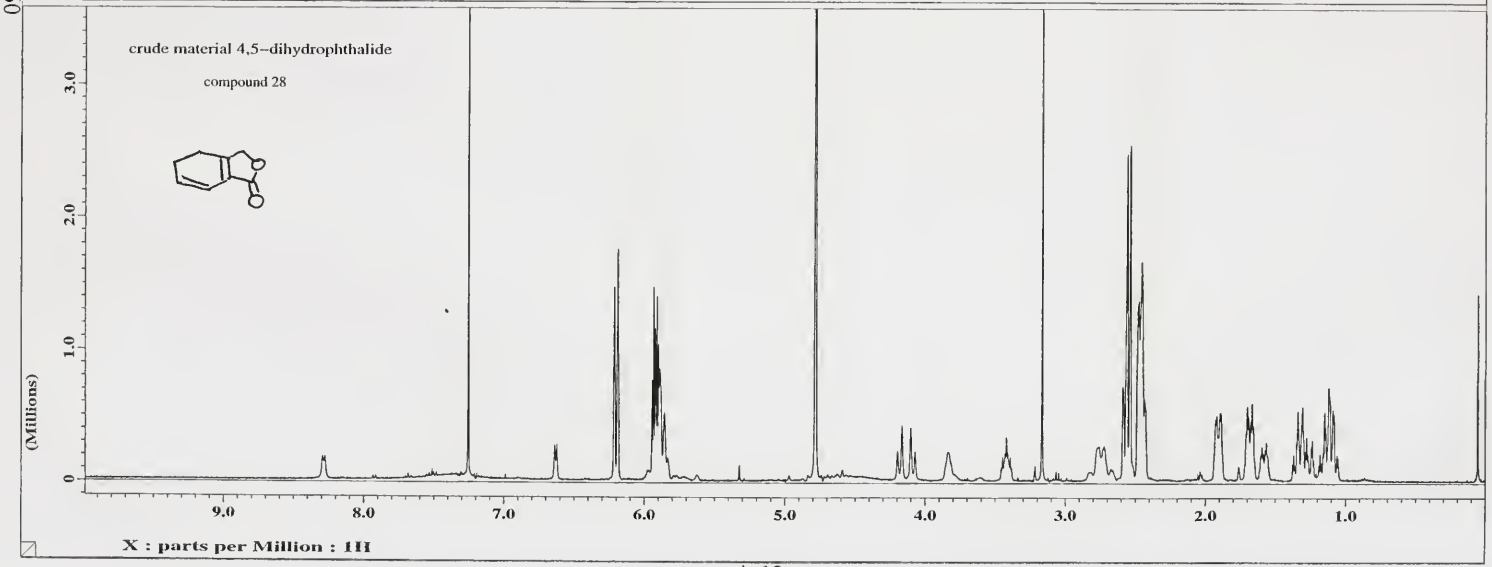

compound 37
13C
OH
ONa
O
(Millions)
20.0
10.0
0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
174.789
133.142
126.163
122.616
122.521
64.455
42.945
26.059
X : parts per Million : 13C

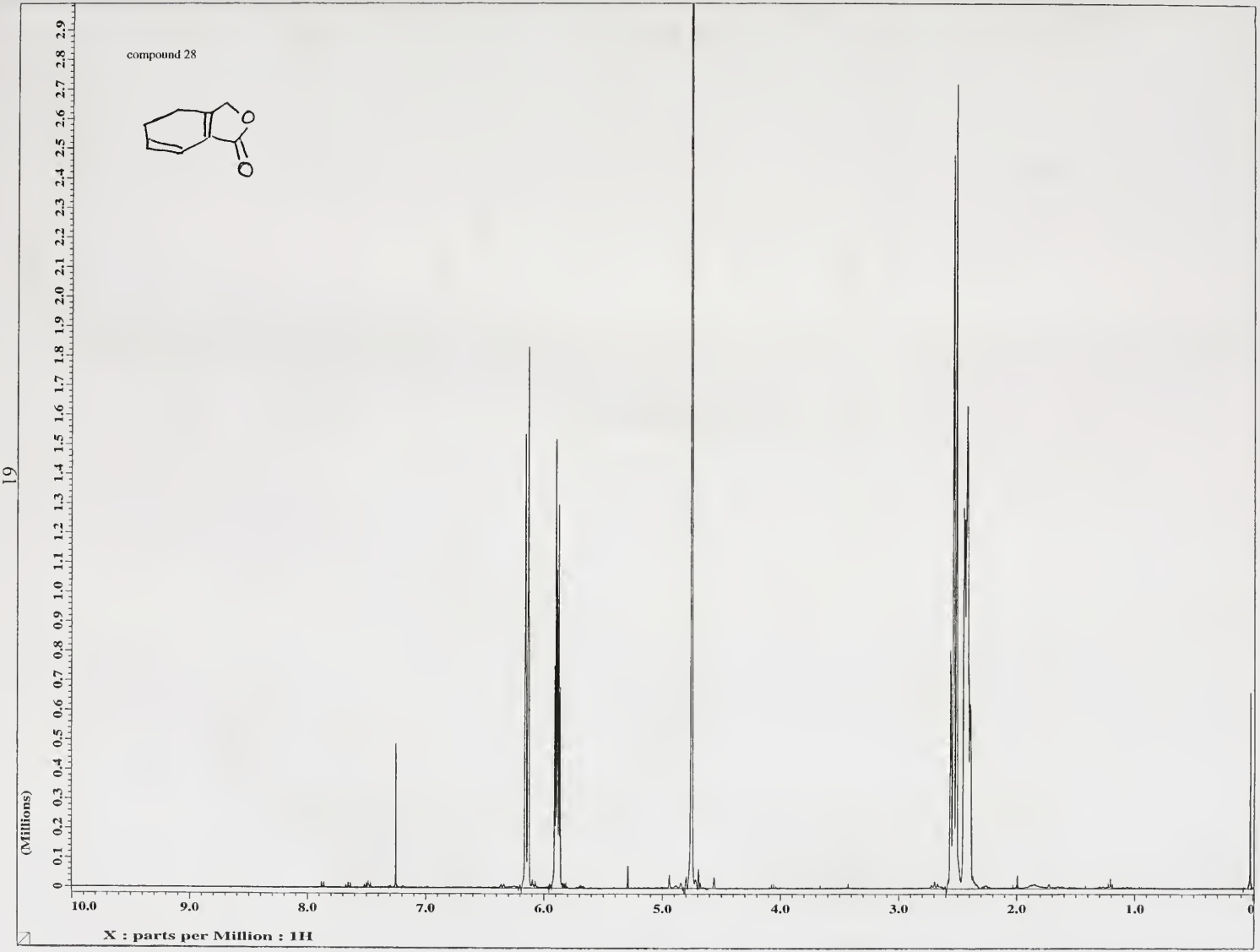

compound 37
DEPT 135
(Millions)
10.0
0
-10.0
-20.0
-30.0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
126.163
122.616
122.521
64.455
42.945
26.059
X : parts per Million : 13C

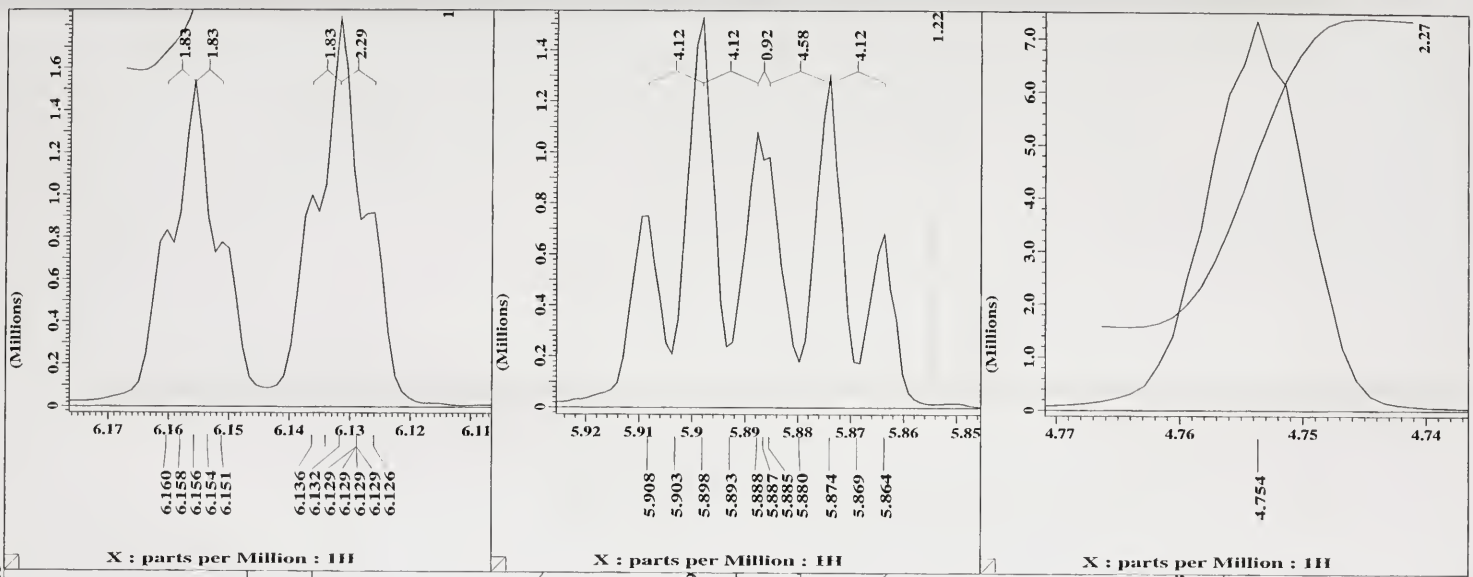

nOe – H–5
compound 37
OH
ONa
O
100.0
0
(Thousands)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H
3.0
2.0
1.0
0
(Millions)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H

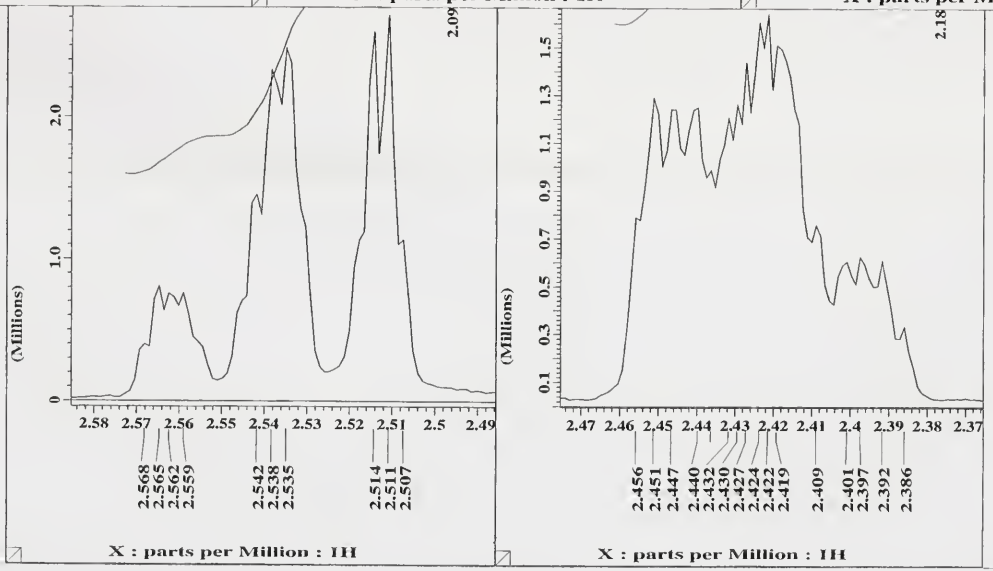

compound 37
OH
ONa
O
(Millions)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H

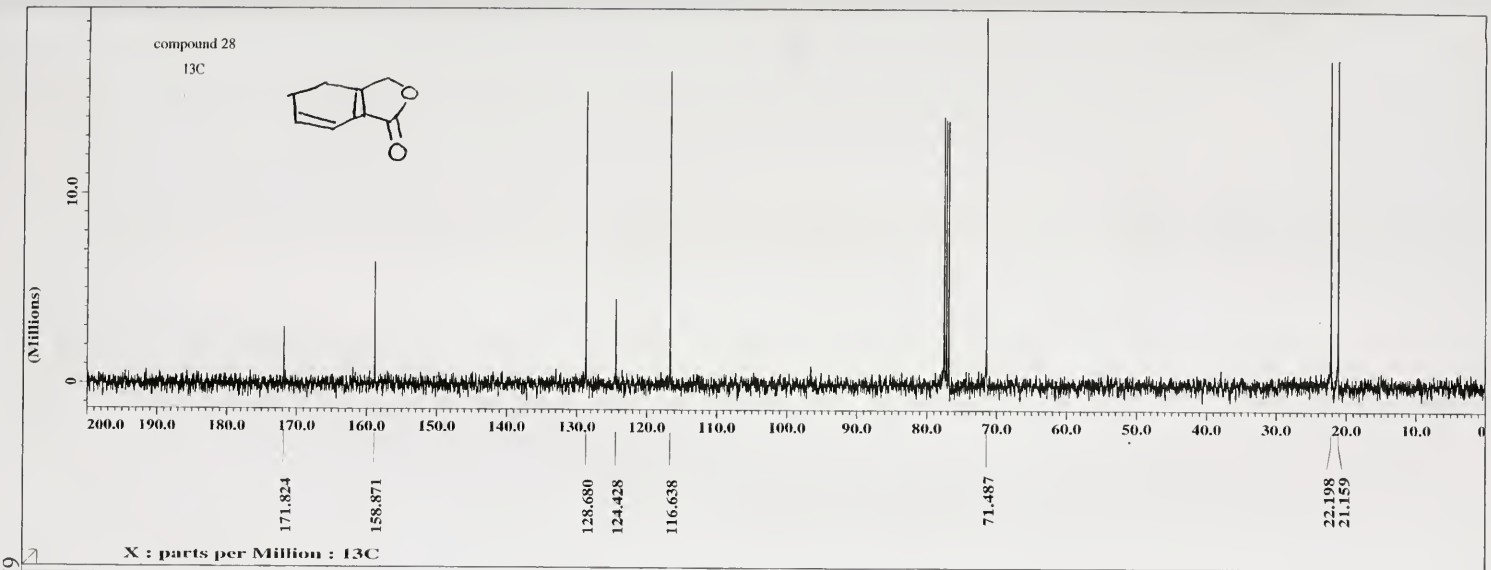
09

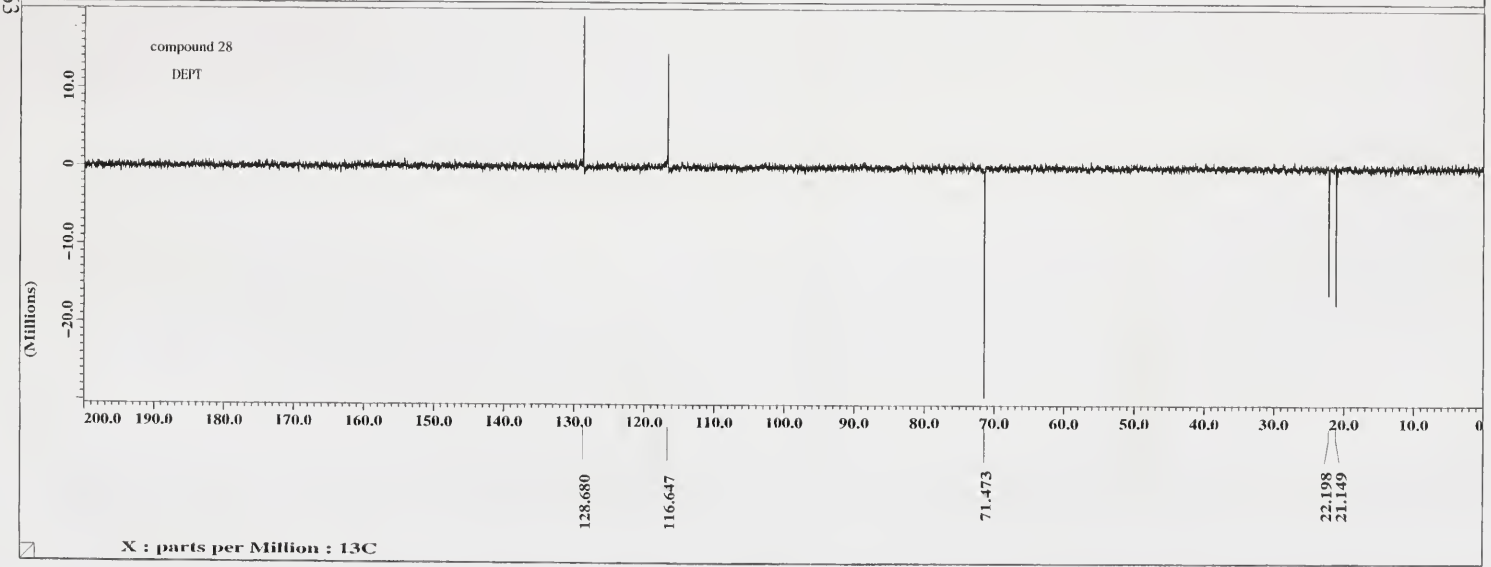

crude material 4,5-dihydrophthalide
compound 28
O
O
(Millions)
3.0
2.0
1.0
0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H

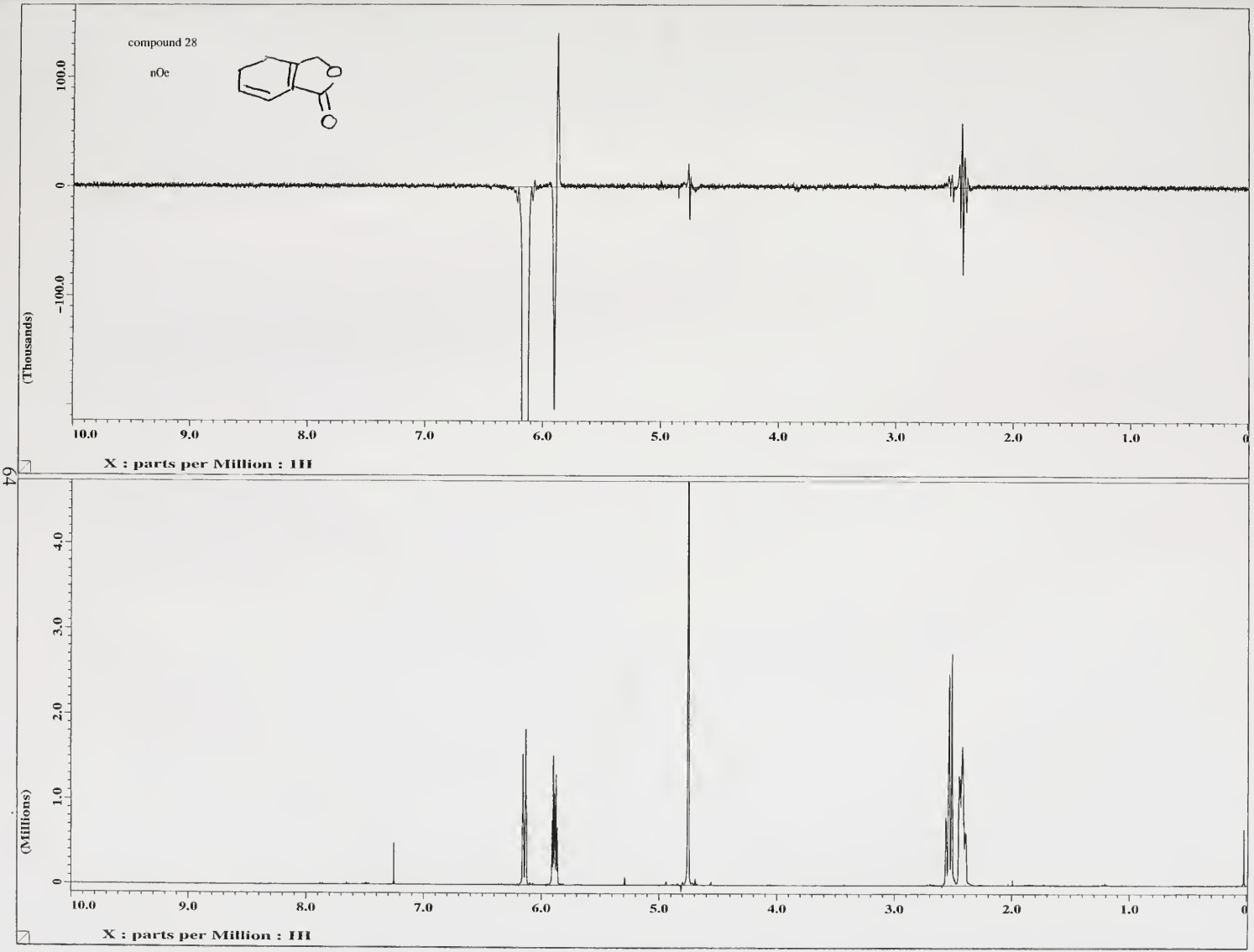

compound 28
(Millions)
X : parts per Million : 1H


1.83
1.83
1.83
2.29
(Millions)
6.17 6.16 6.15 6.14 6.13 6.12 6.11
6.160 6.158 6.156 6.154 6.151 6.136 6.132 6.129 6.129 6.129 6.129 6.126
X : parts per Million : 1H
4.12
4.12
0.92
4.58
4.12
1.22
(Millions)
5.92 5.91 5.9 5.89 5.88 5.87 5.86 5.85
5.908 5.903 5.898 5.893 5.888 5.887 5.885 5.880 5.874 5.869 5.864
X : parts per Million : 1H
2.27
(Millions)
4.77 4.76 4.75 4.74
4.754
X : parts per Million : 1H

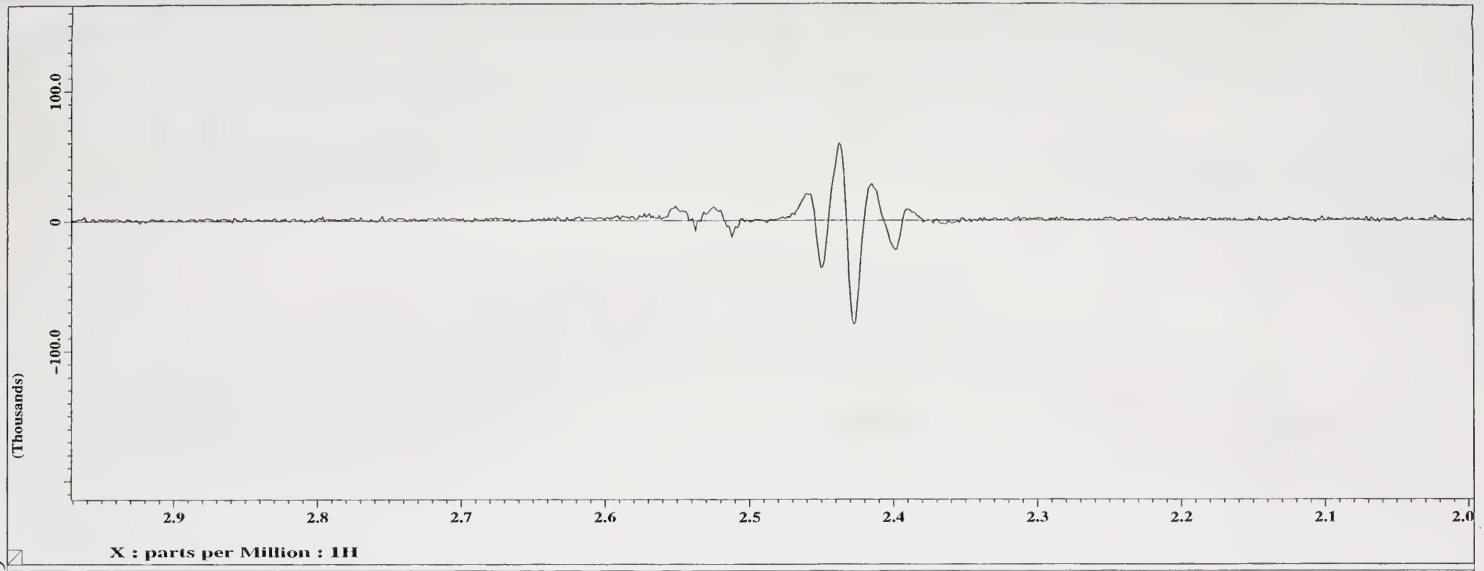

2.09
(Millions)
2.58 2.57 2.56 2.55 2.54 2.53 2.52 2.51 2.5 2.49
2.568 2.565 2.562 2.559 2.542 2.538 2.535 2.514 2.511 2.507
X : parts per Million : 1H
2.18
(Millions)
2.47 2.46 2.45 2.44 2.43 2.42 2.41 2.4 2.39 2.38 2.37
2.456 2.451 2.447 2.440 2.432 2.430 2.427 2.424 2.422 2.419 2.409 2.401 2.397 2.392 2.386
X : parts per Million : 1H

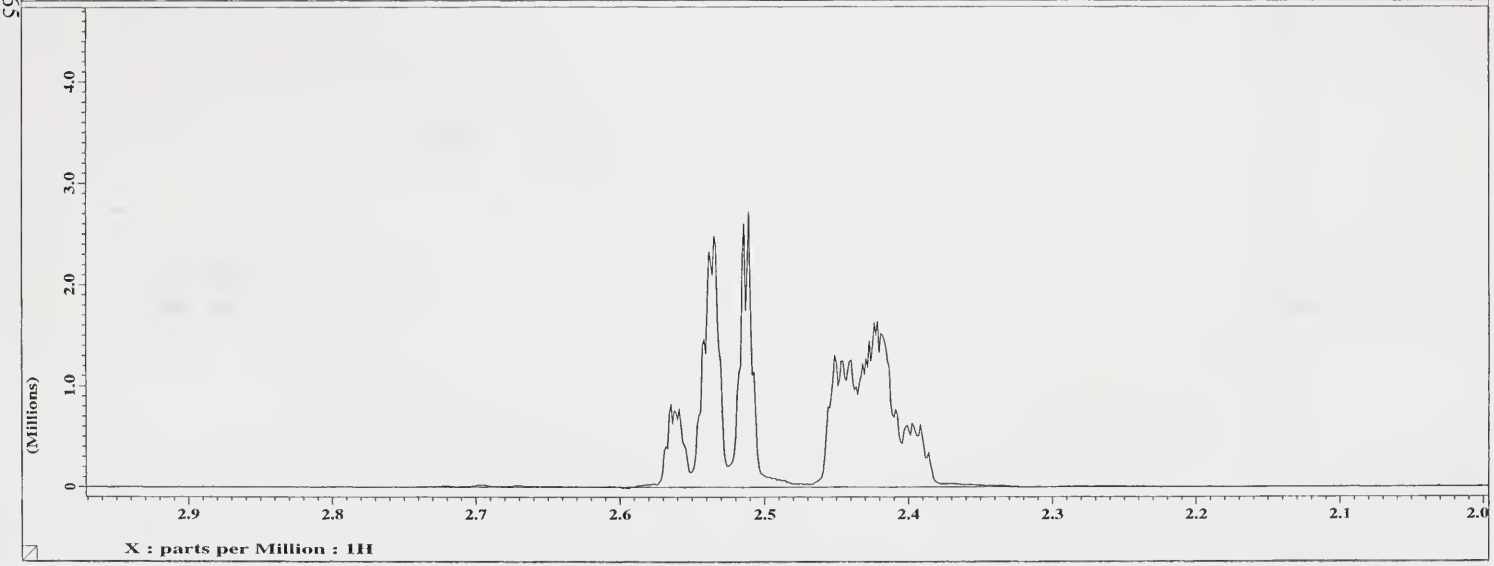

compound 28
13C
(Millions)
10.0
0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0
171.824
158.871
128.680
124.428
116.638
71.487
22.198
21.159
X : parts per Million : 13C

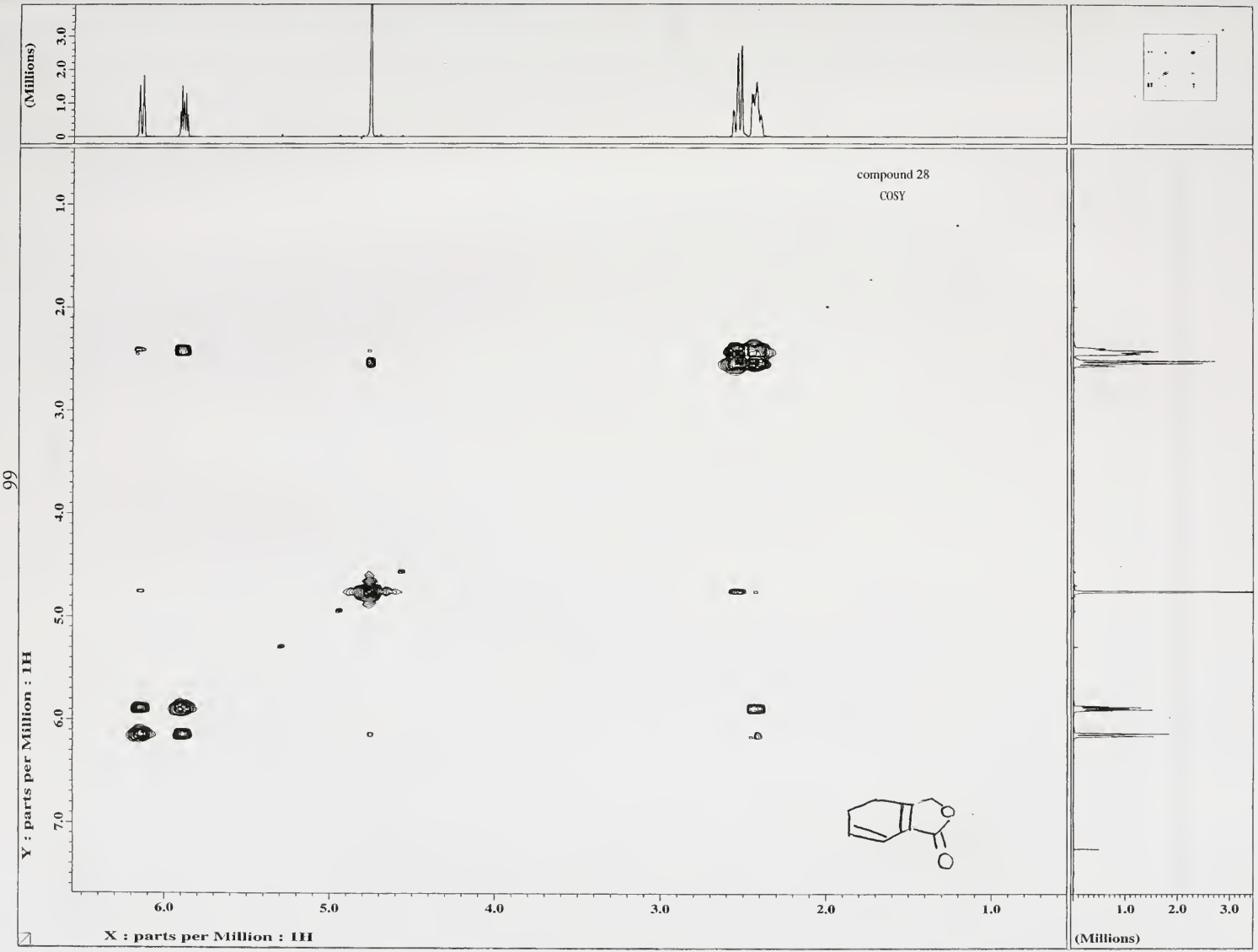

compound 28
DEPT
(Millions)
10.0
0
-10.0
-20.0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0
128.680
116.647
71.473
22.198
21.149
X : parts per Million : 13C

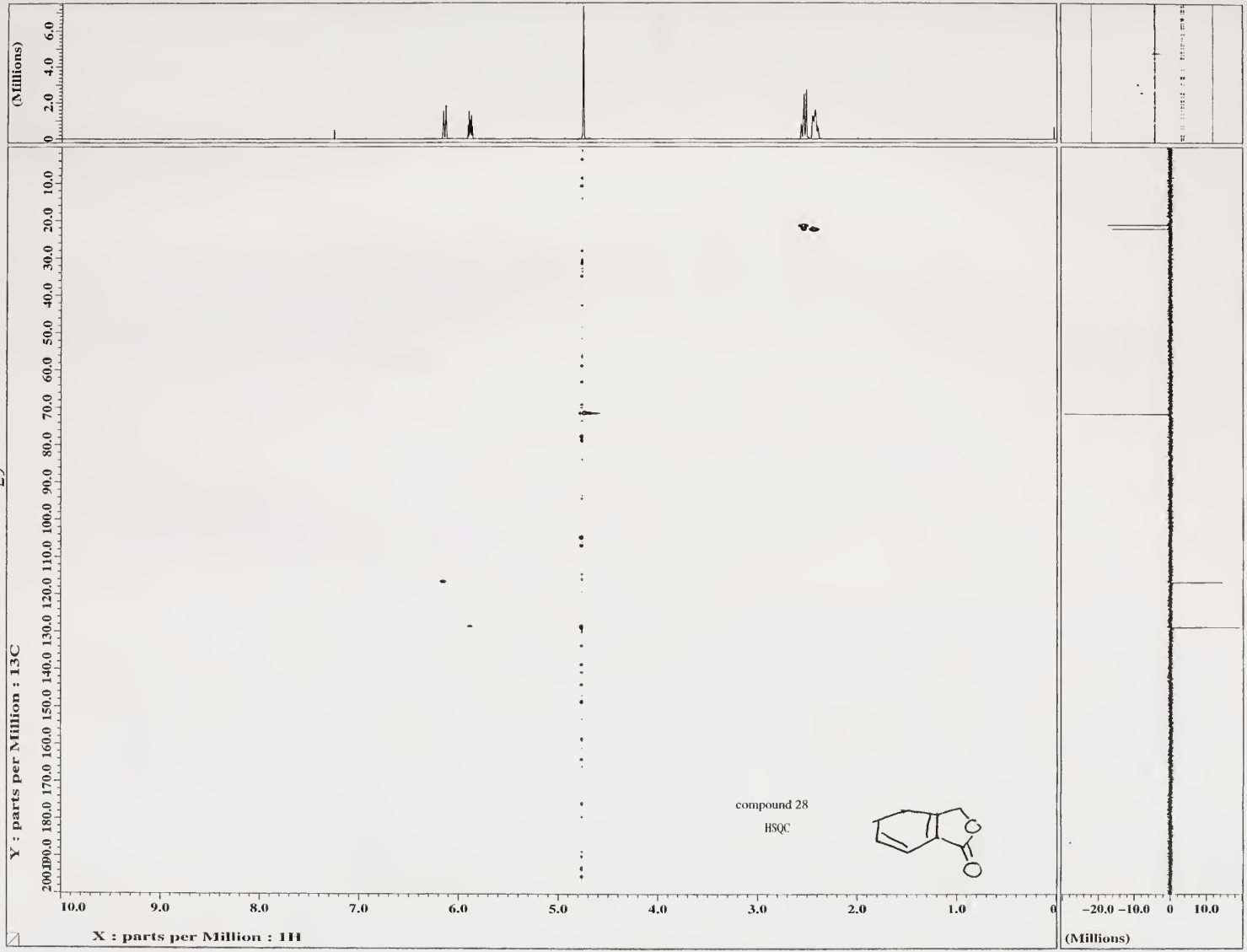

compound 28
nOe
100.0
0
-100.0
(Thousands)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H
4.0
3.0
2.0
1.0
0
(Millions)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H

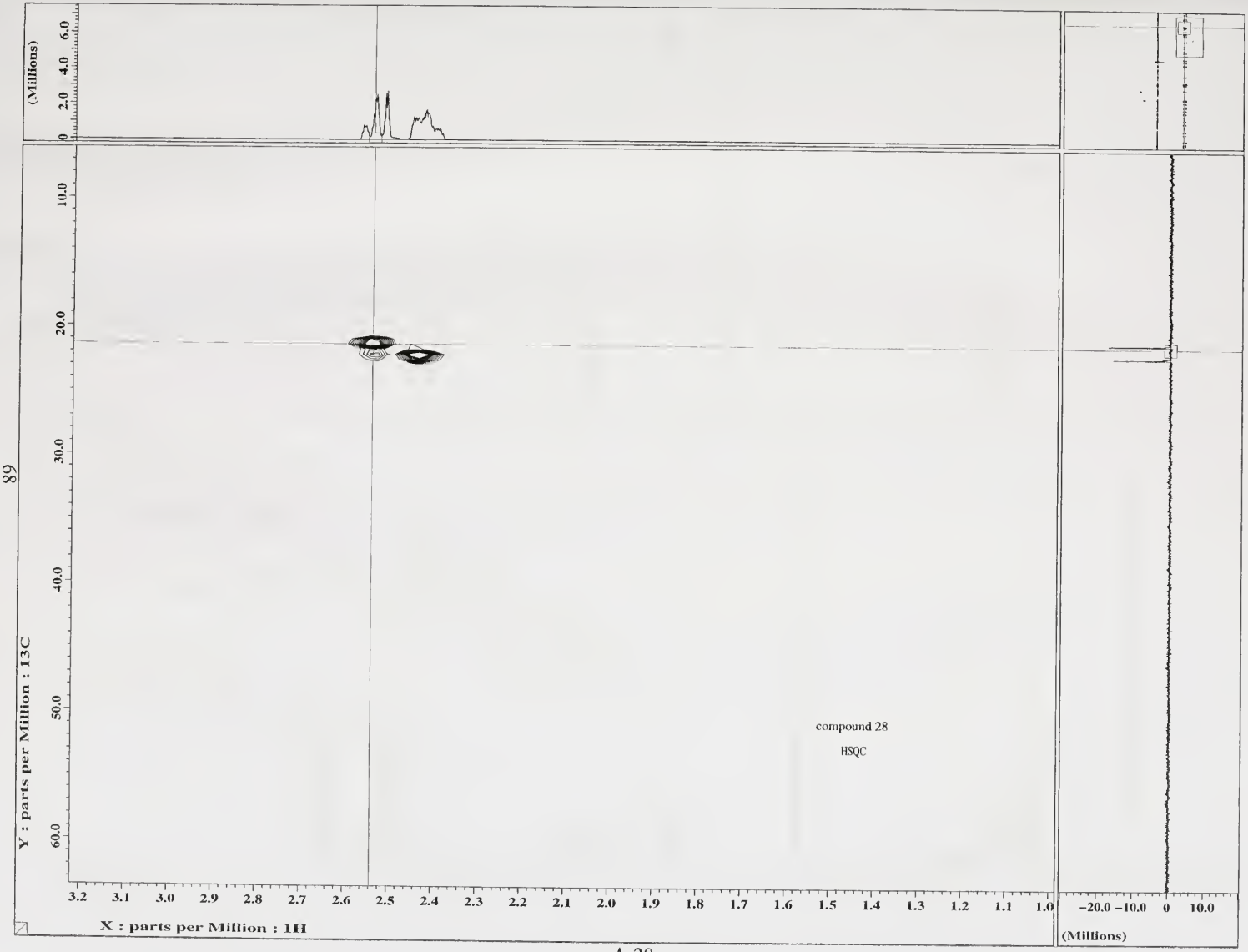
64

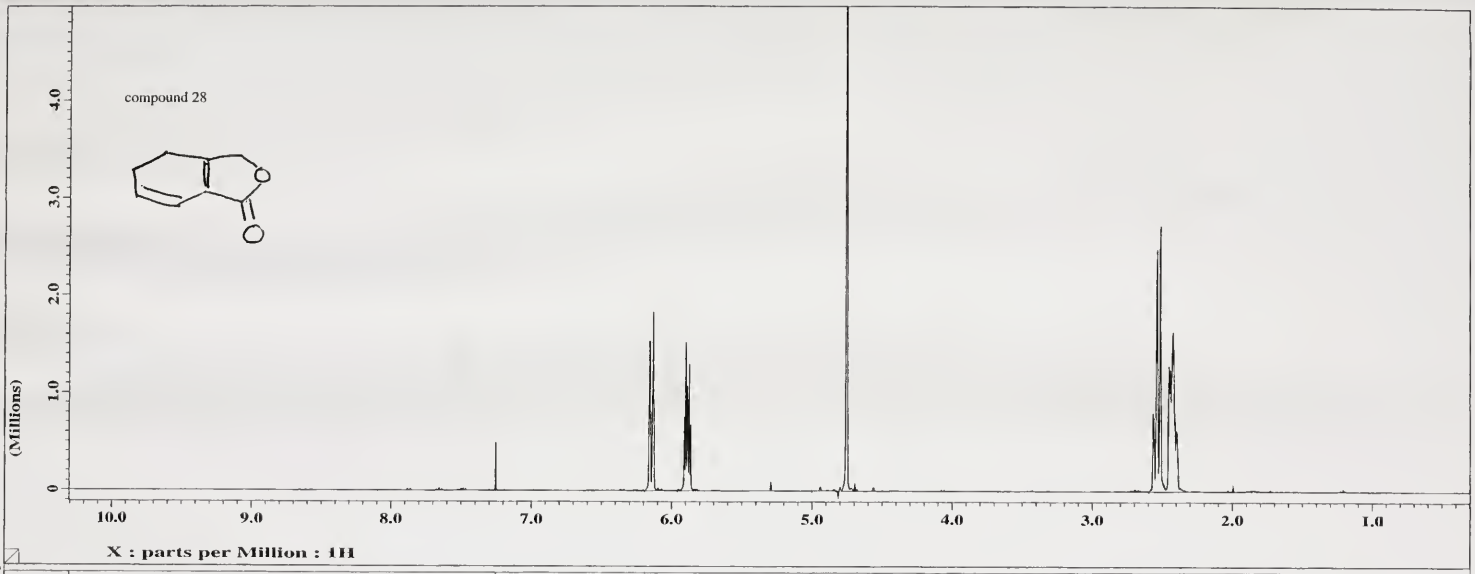

100.0
0
-100.0
(Thousands)
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
X : parts per Million : 1H

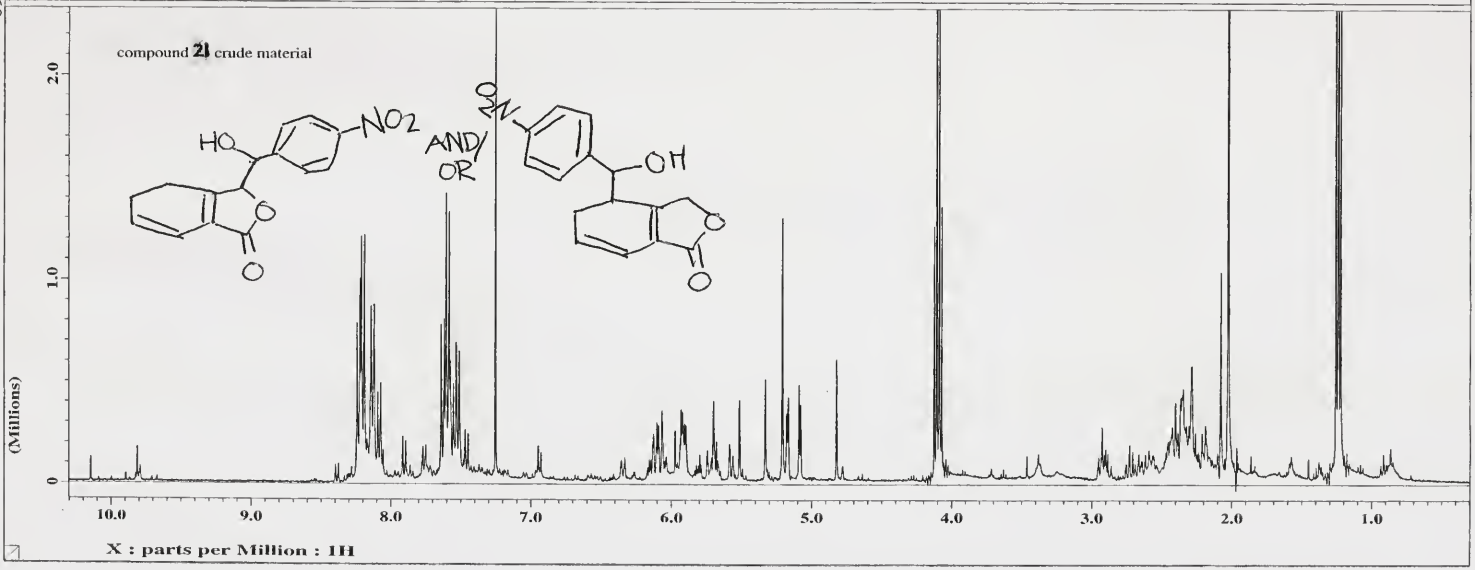

4.0
3.0
2.0
1.0
0
(Millions)
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
X : parts per Million : 1H

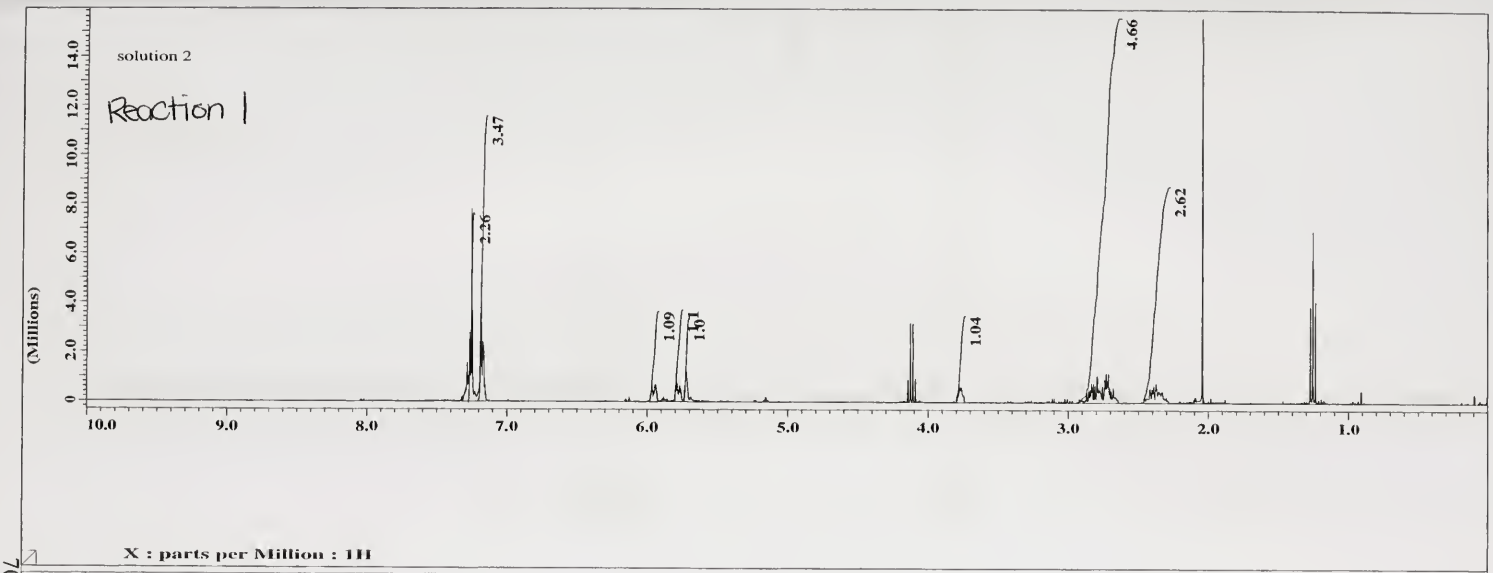

compound 28
COSY
(Millions)
Y : parts per Million : 1H
X : parts per Million : 1H
(Millions)

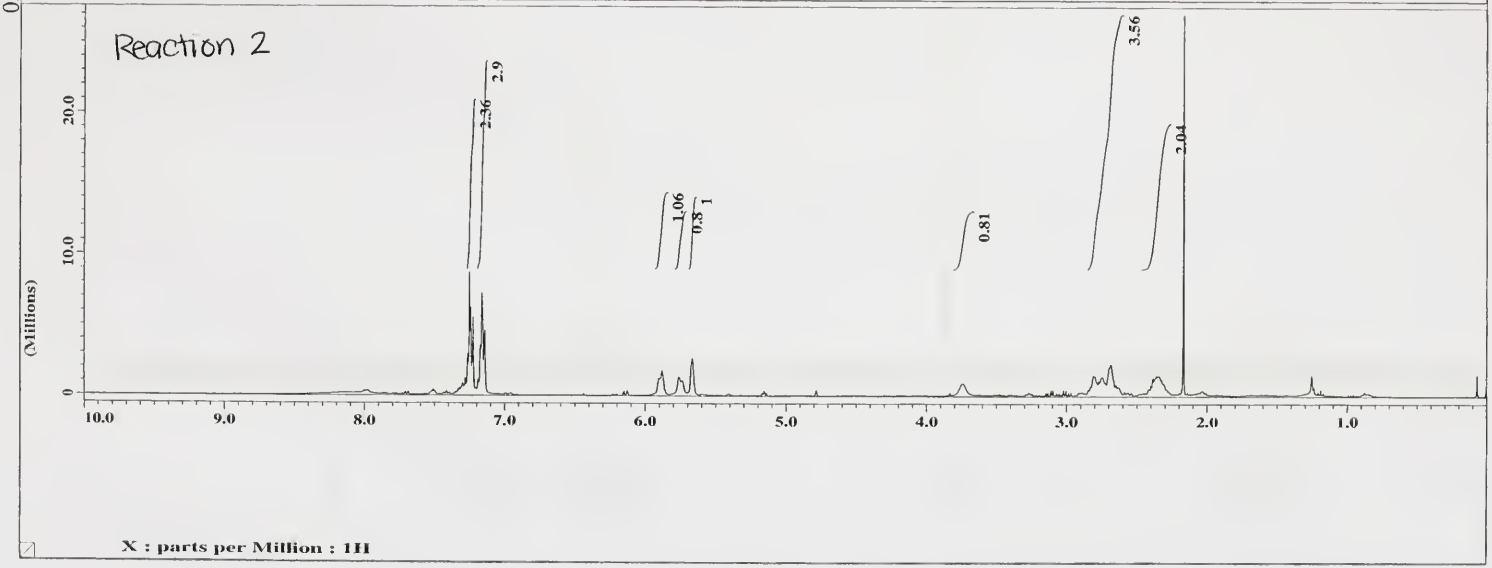

(Millions)
0
2.0
4.0
6.0
Y : parts per Million : 13C
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
170.0
180.0
190.0
200.0
compound 28
HSQC
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
X : parts per Million : 1H
-20.0 -10.0
0
10.0
(Millions)

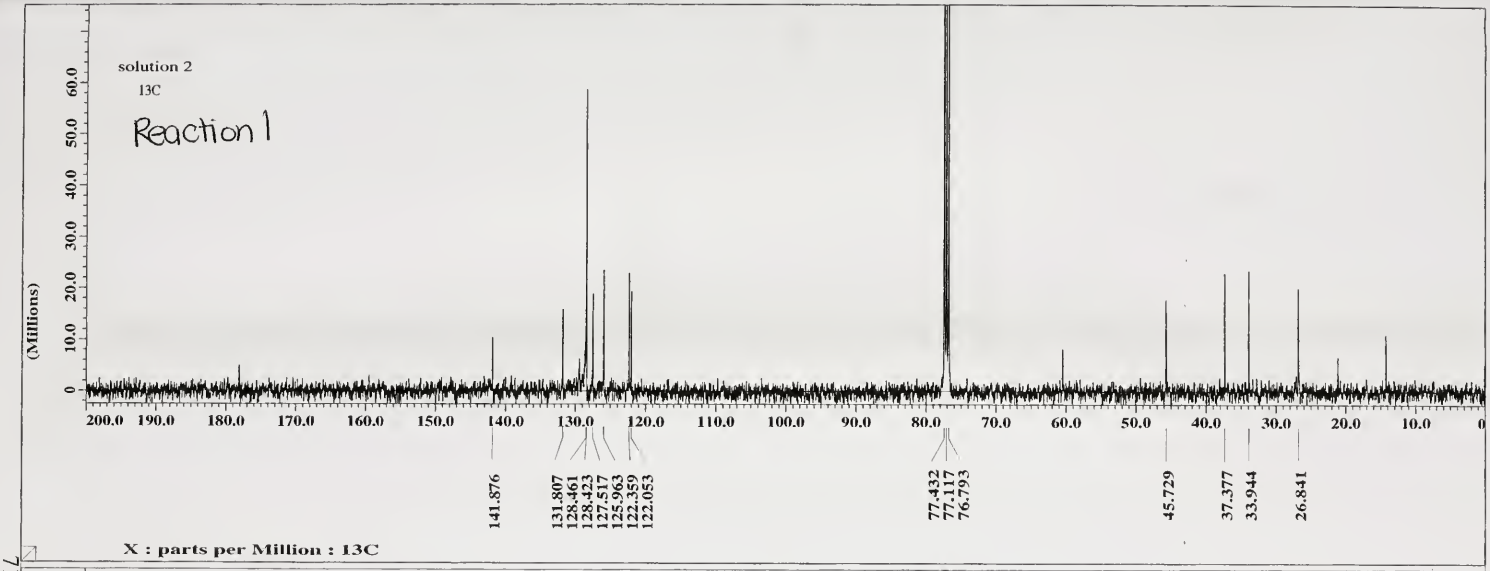

(Millions)
0
2.0
4.0
6.0
10.0
20.0
30.0
40.0
50.0
60.0
Y : parts per Million : 13C
compound 28
HSQC
3.2
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
X : parts per Million : 1H
−20.0 −10.0
0
10.0
(Millions)

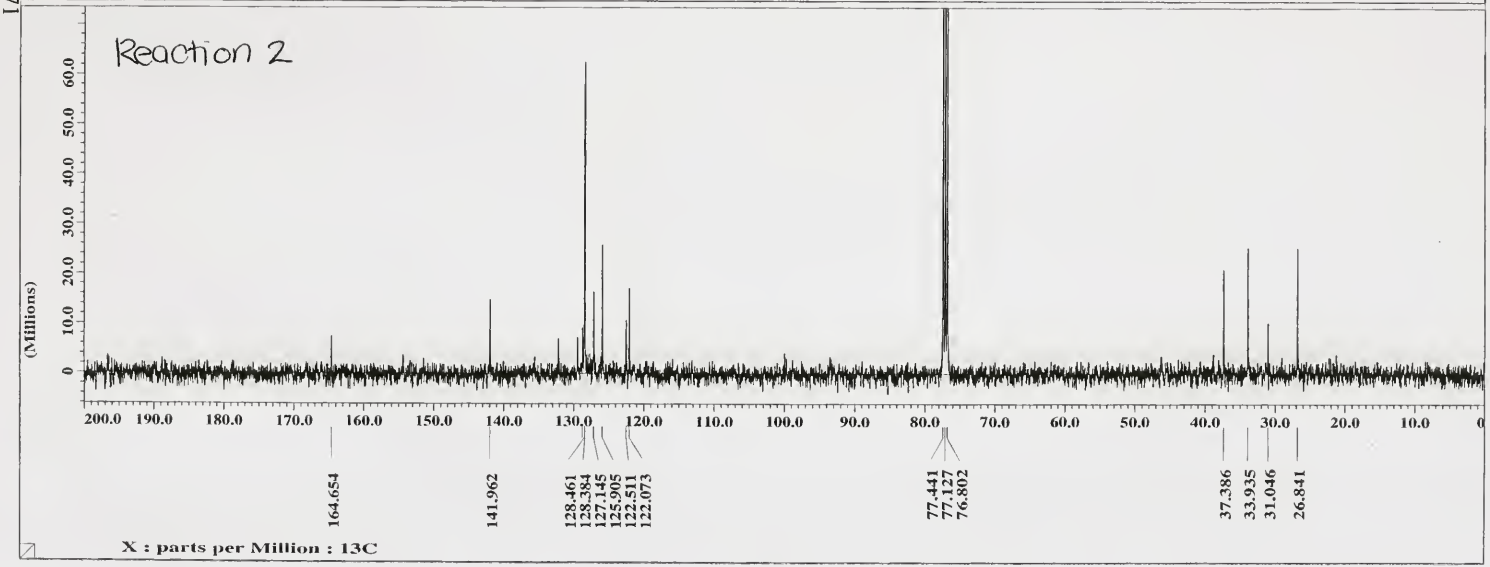

compound 28
(Millions)
4.0
3.0
2.0
1.0
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H

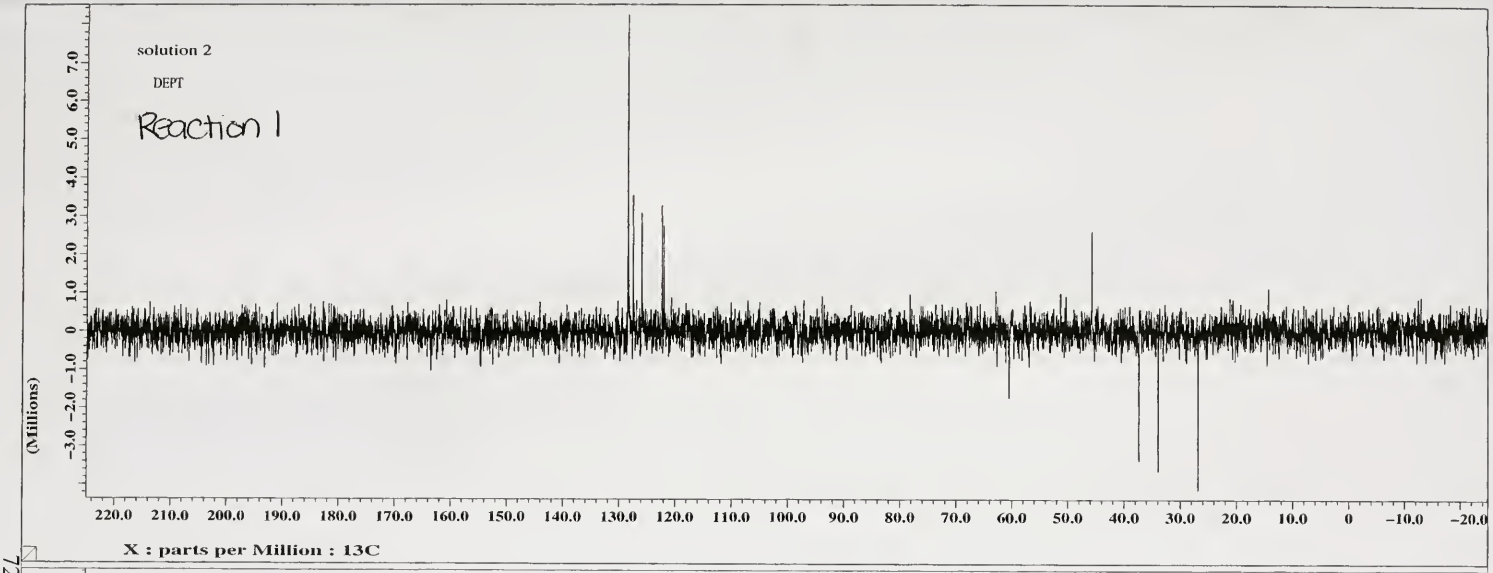

compound 21 crude material
HO
NO2
AND/
OR
O2N
OH
(Millions)
2.0
1.0
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H

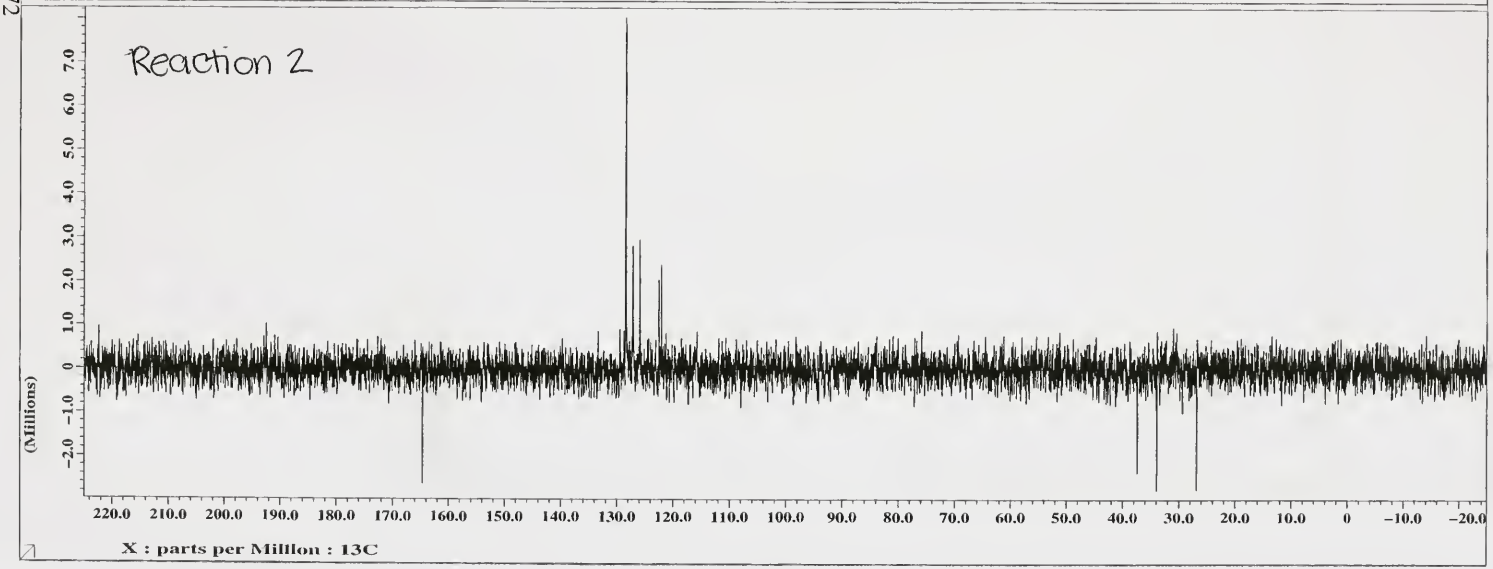

solution 2
Reaction 1
(Millions)
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0
3.47
2.26
1.09
1.01
1.04
4.66
2.62
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H

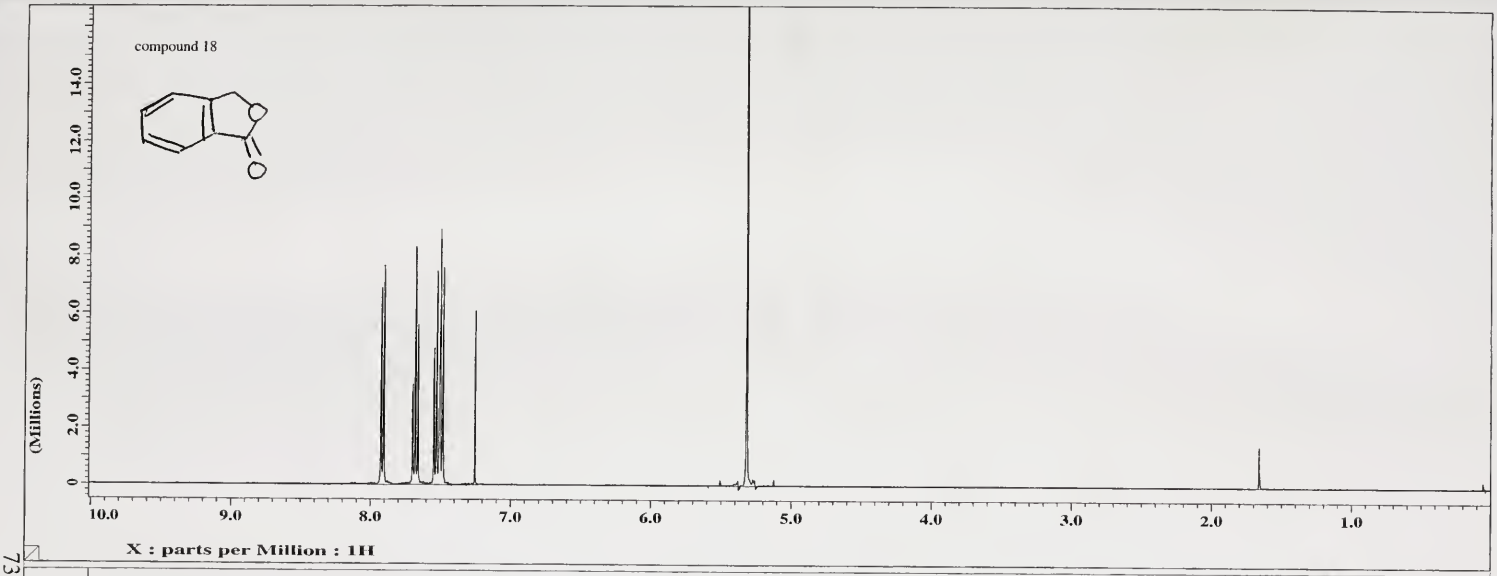

Reaction 2
(Millions)
20.0
10.0
0
2.9
2.36
1.06
0.8
1
0.81
3.56
2.04
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H

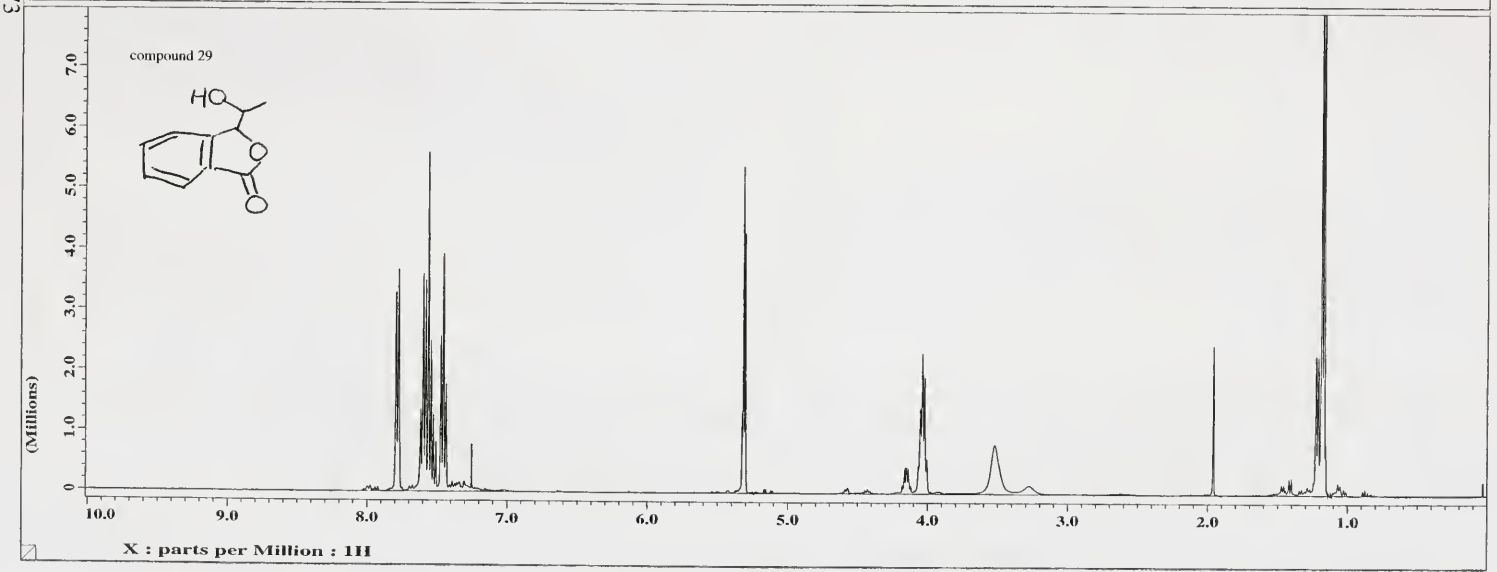

solution 2
13C
Reaction 1
(Millions)
60.0
50.0
40.0
30.0
20.0
10.0
0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0
141.876
131.807
128.461
128.423
127.517
125.963
122.359
122.053
77.432
77.117
76.793
45.729
37.377
33.944
26.841
X : parts per Million : 13C

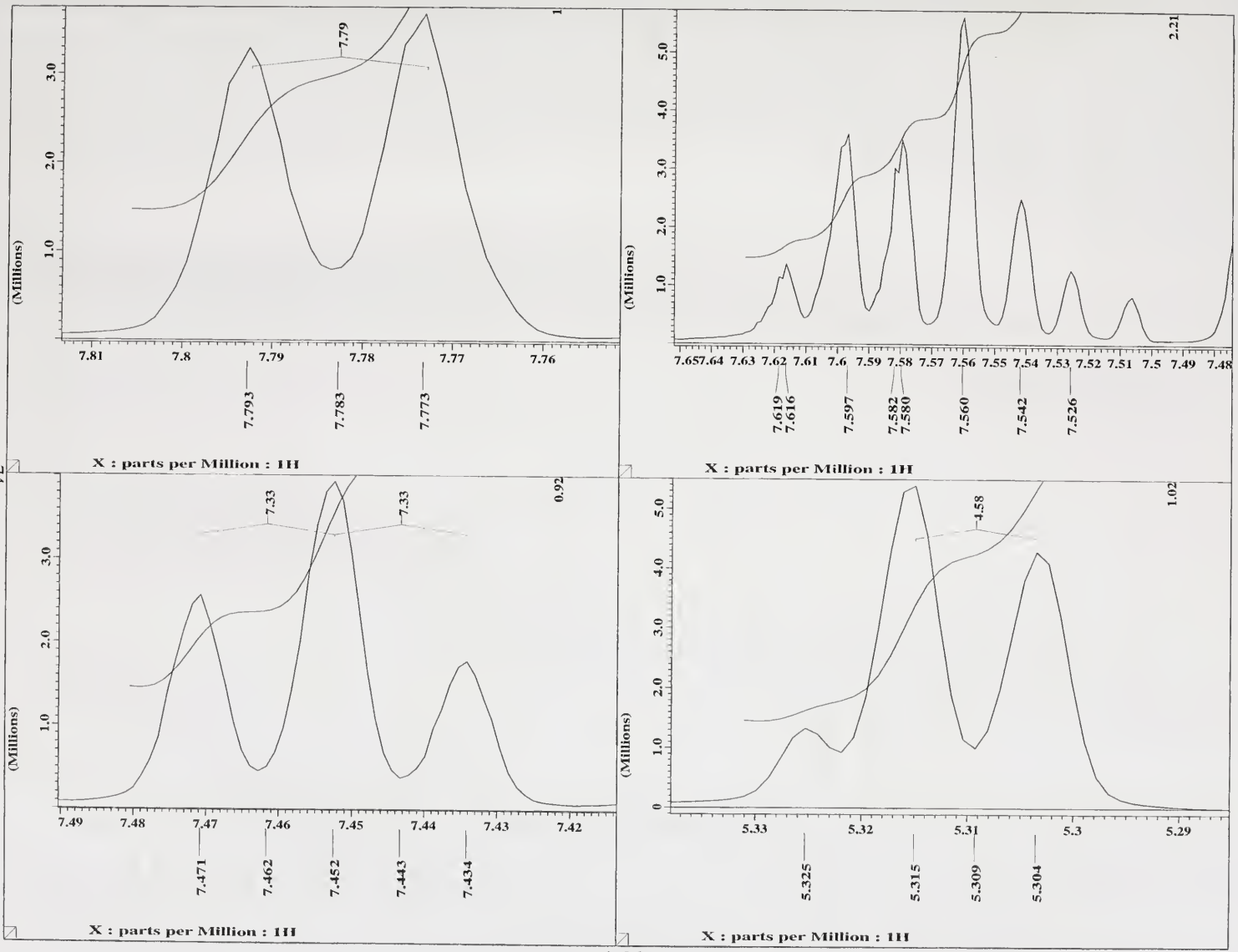

Reaction 2
(Millions)
60.0
50.0
40.0
30.0
20.0
10.0
0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0
164.654
141.962
128.461
128.384
127.145
125.905
122.511
122.073
77.441
77.127
76.802
37.386
33.935
31.046
26.841
X : parts per Million : 13C


solution 2
DEPT
Reaction 1
(Millions)
X : parts per Million : 13C

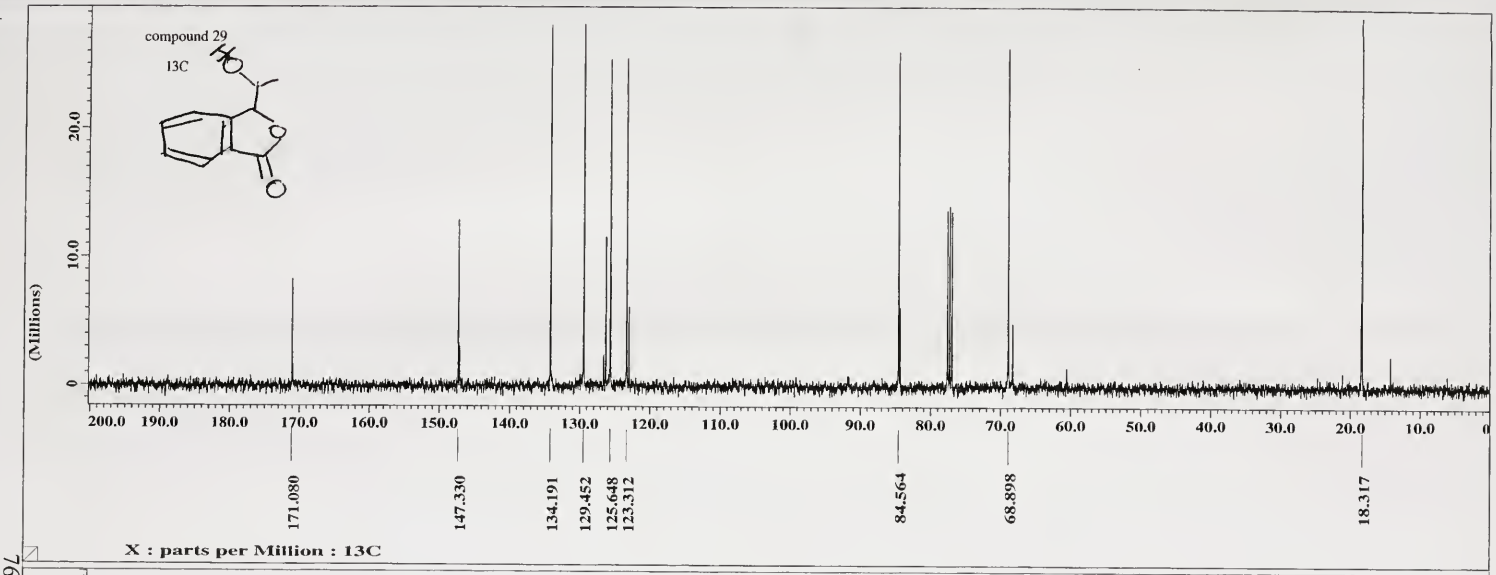

Reaction 2
(Millions)
X : parts per Million : 13C

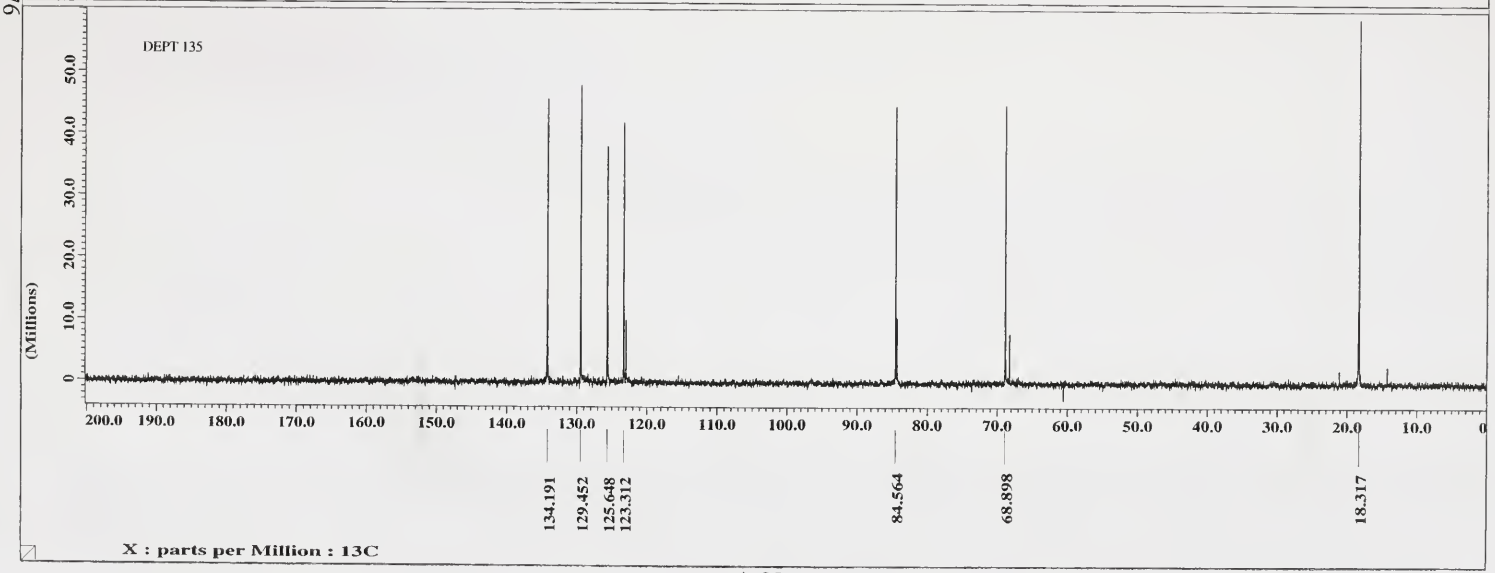

compound 18
(Millions)
0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H

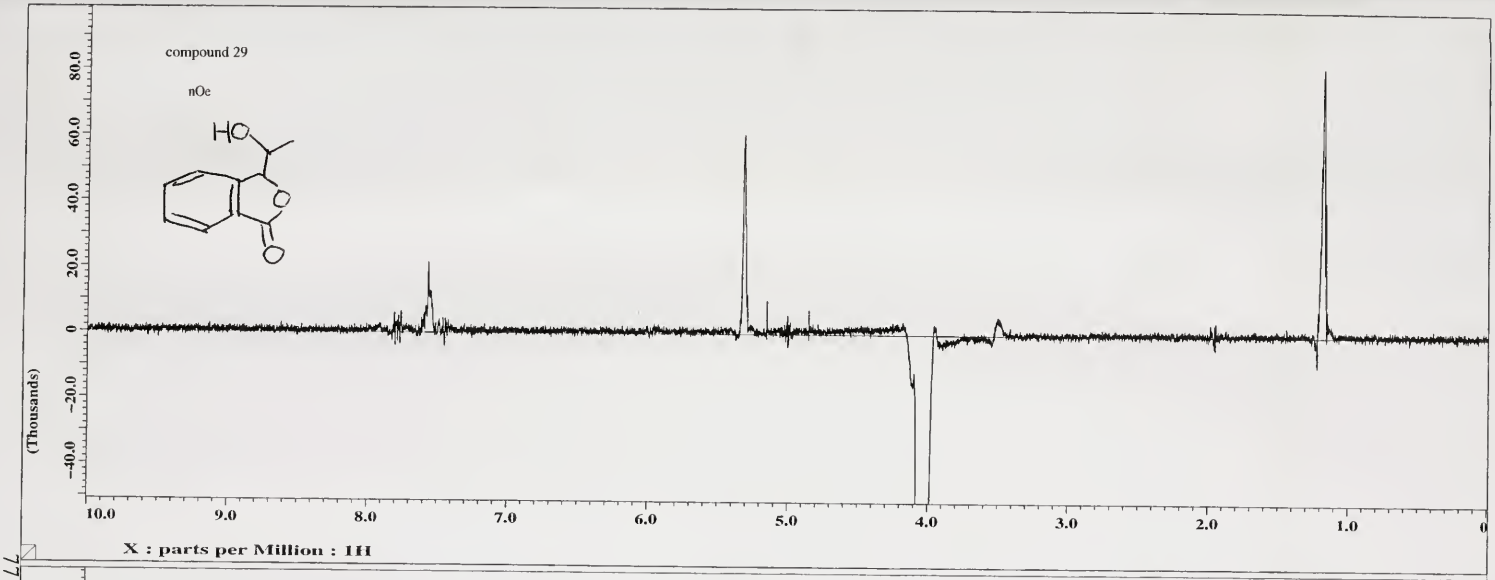

compound 29
HO
(Millions)
0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H

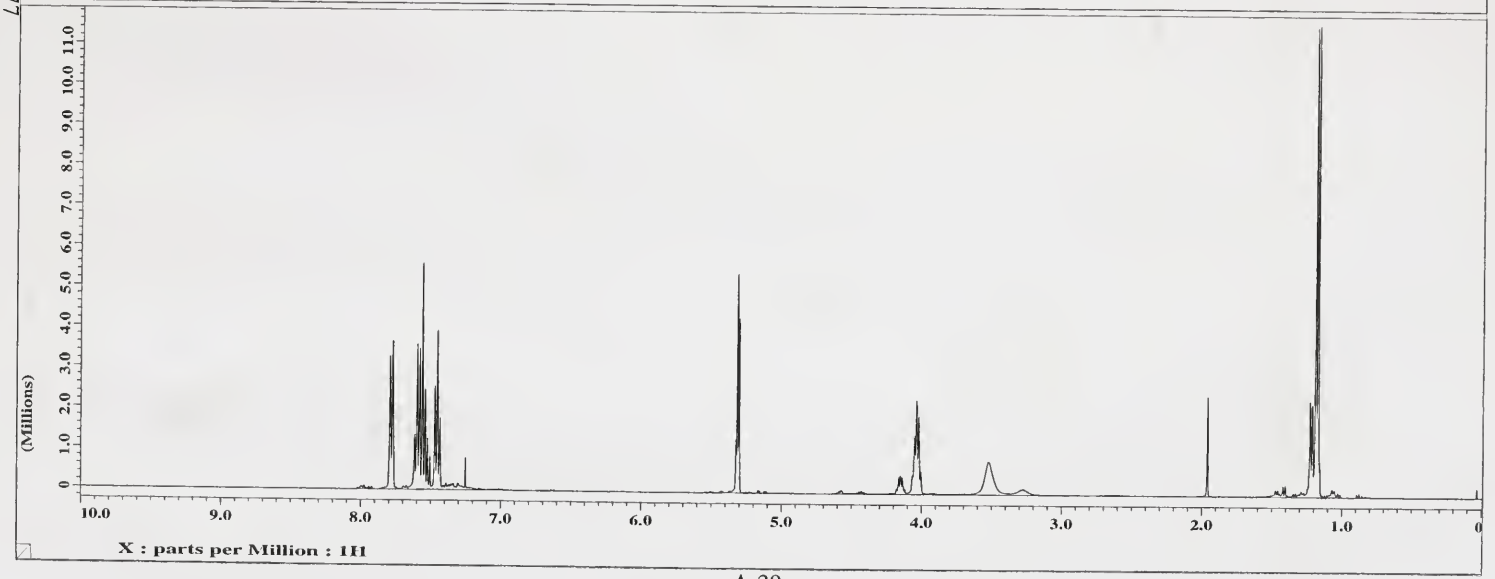

7.79
(Millions)
7.81 7.8 7.79 7.78 7.77 7.76
7.793
7.783
7.773
X : parts per Million : 1H
2.21
(Millions)
7.657.64 7.63 7.62 7.61 7.6 7.59 7.58 7.57 7.56 7.55 7.54 7.53 7.52 7.51 7.5 7.49 7.48
7.619
7.616
7.597
7.582
7.580
7.560
7.542
7.526
X : parts per Million : 1H
7.33
7.33
0.92
(Millions)
7.49 7.48 7.47 7.46 7.45 7.44 7.43 7.42
7.471
7.462
7.452
7.443
7.434
X : parts per Million : 1H
4.58
1.02
(Millions)
5.33 5.32 5.31 5.3 5.29
5.325
5.315
5.309
5.304
X : parts per Million : 1H

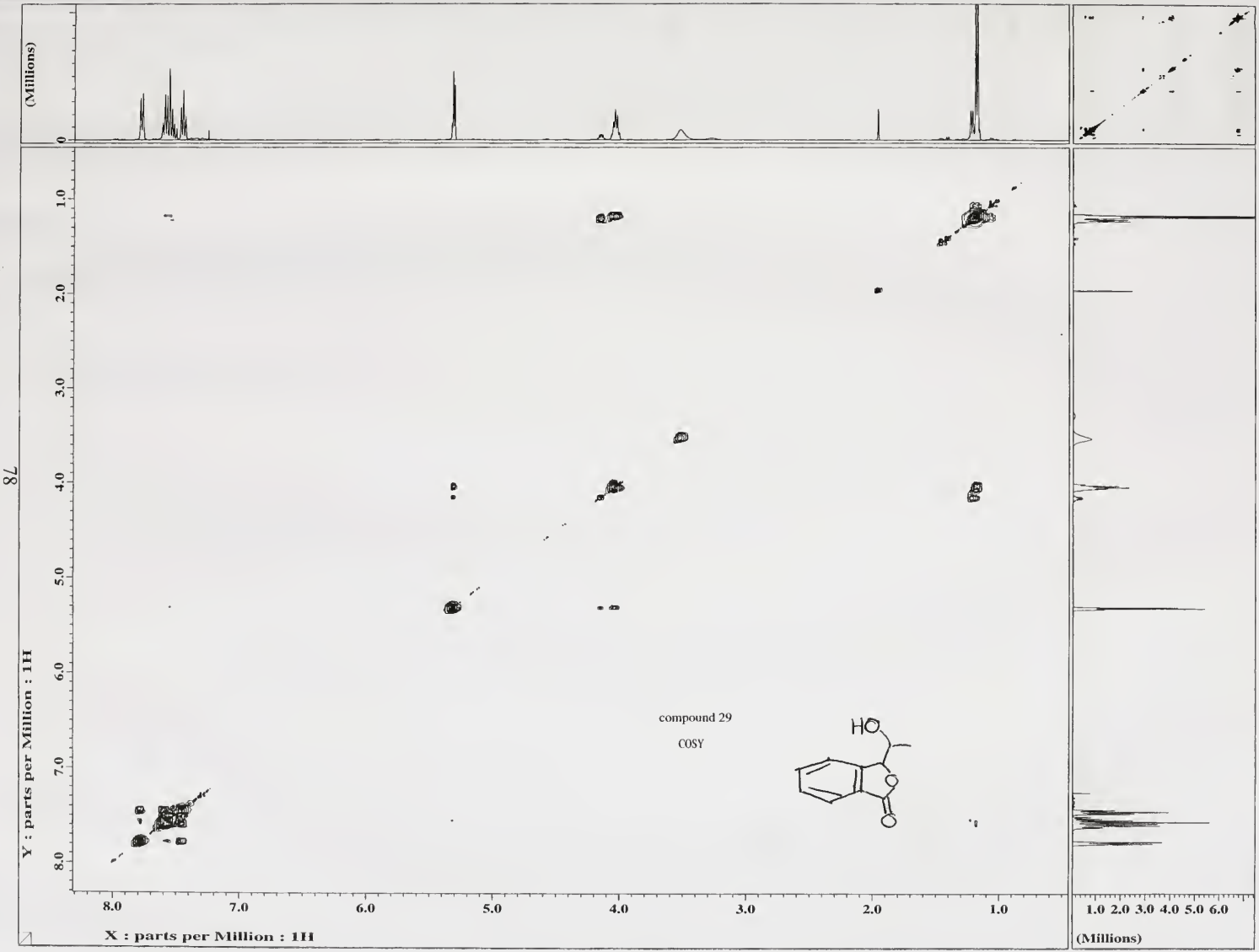
(Millions)
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0 2.1 2.2 2.3
5.95
5.04
6.41
6.87
1.0
X : parts per Million : 1H
4.08 4.07 4.06 4.05 4.04 4.03 4.02 4.01 4.0 3.99 3.98
4.065
4.058
4.050
4.044
4.038
4.030
4.022
4.013
4.005
(Thousands)
100.0 200.0 300.0 400.0 500.0 600.0 700.0
0.62
X : parts per Million : 1H
3.6 3.58 3.56 3.54 3.52 3.5 3.48 3.46 3.44
(Millions)
0 1.0 2.0 3.0 4.0 5.0 6.0 7.0 8.0 9.0 10.0 11.0
6.41
2.62
X : parts per Million : 1H
1.2 1.19 1.18 1.17 1.16
1.189
1.181
1.173


compound 29
13C
(Millions)
0
10.0
20.0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0
171.080
147.330
134.191
129.452
125.648
123.312
84.564
68.898
18.317
X : parts per Million : 13C

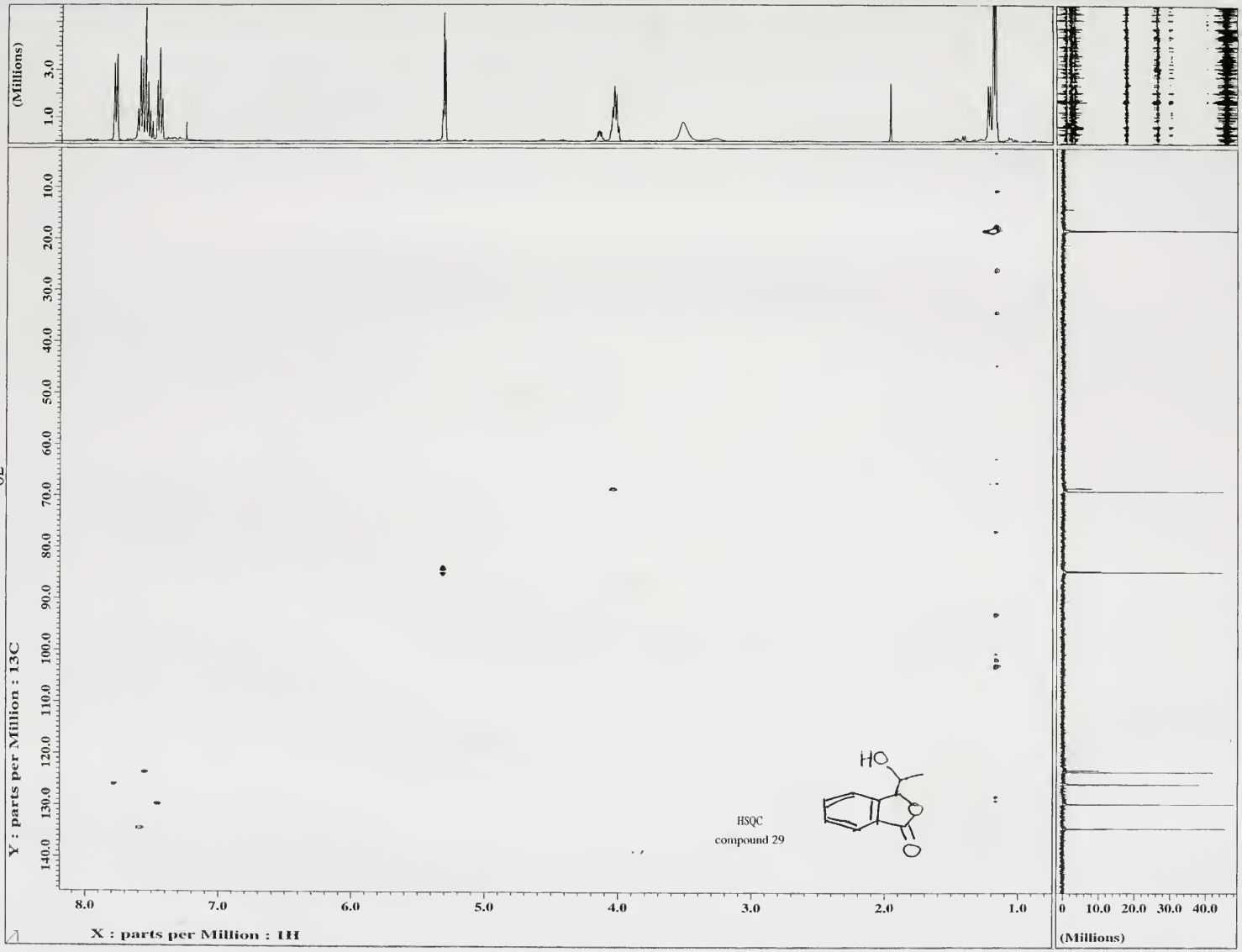

DEPT 135
(Millions)
0
10.0
20.0
30.0
40.0
50.0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0
134.191
129.452
125.648
123.312
84.564
68.898
18.317
X : parts per Million : 13C

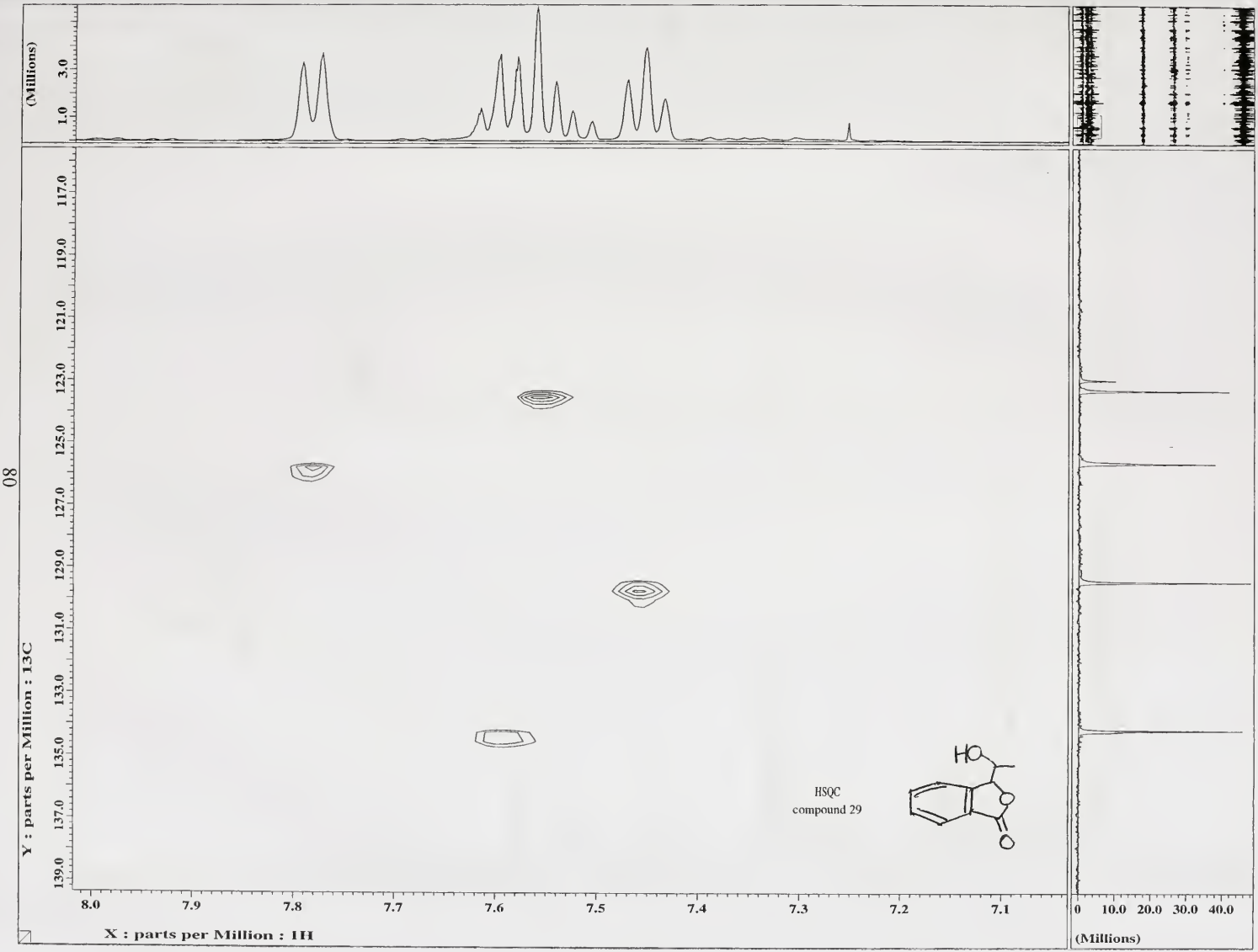

compound 29
nOe
HO
O
O
(Thousands)
80.0
60.0
40.0
20.0
0
-20.0
-40.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
X : parts per Million : 1H

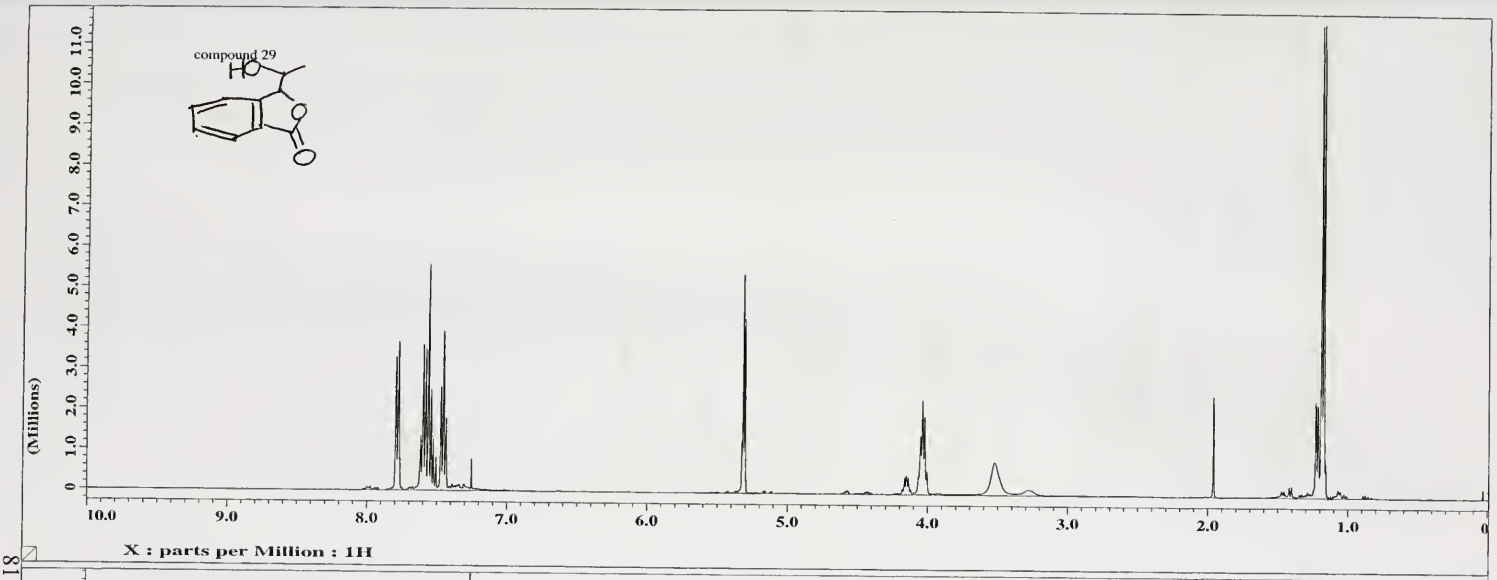

(Millions)
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
X : parts per Million : 1H

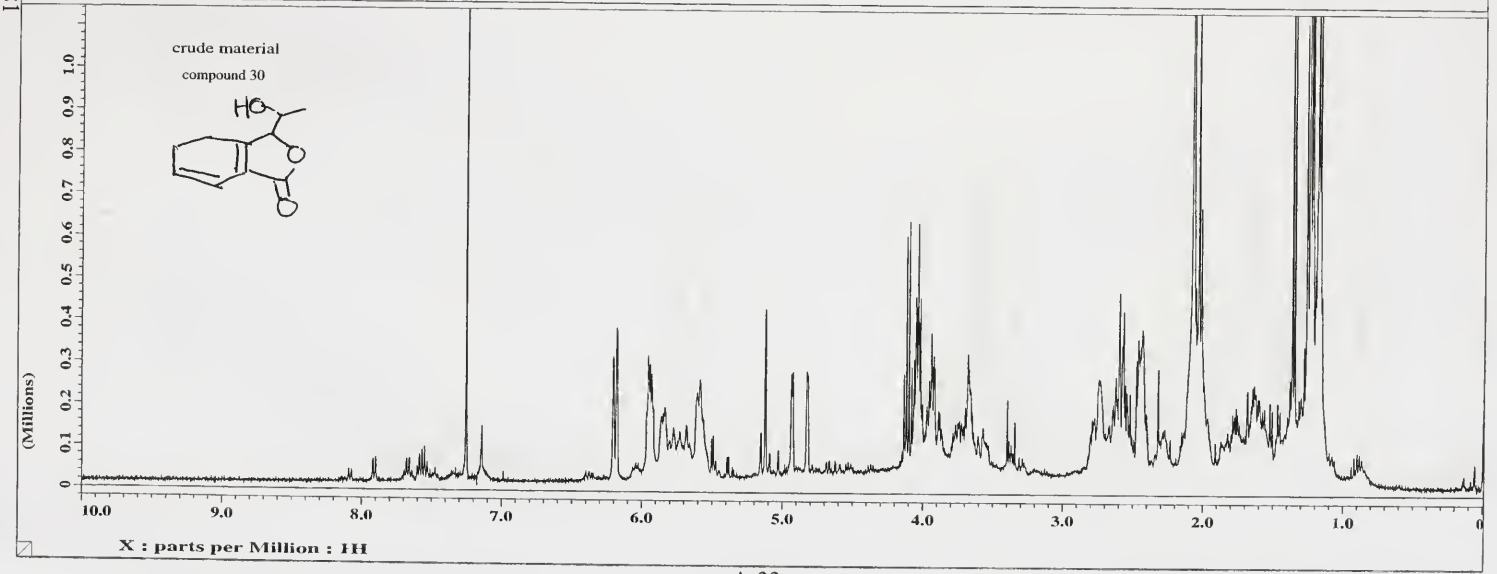

(Millions)
0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
Y : parts per Million : 1H
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H
compound 29
COSY
HO
O
O
1.0 2.0 3.0 4.0 5.0 6.0
(Millions)

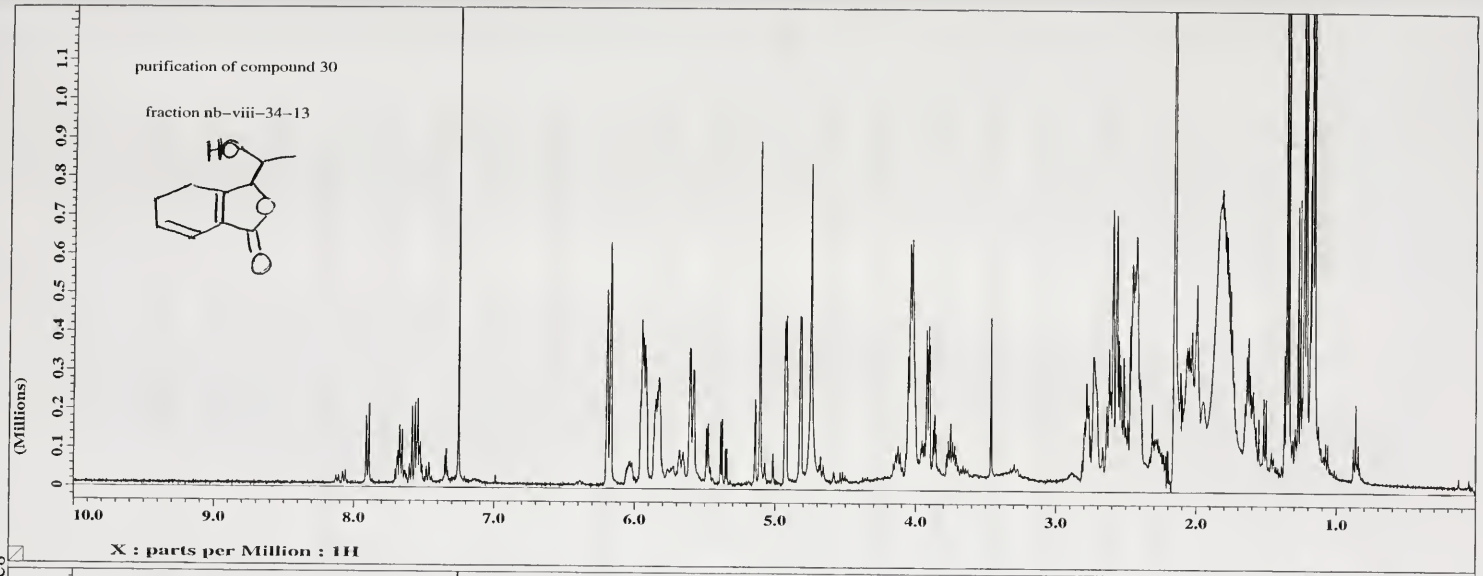
78

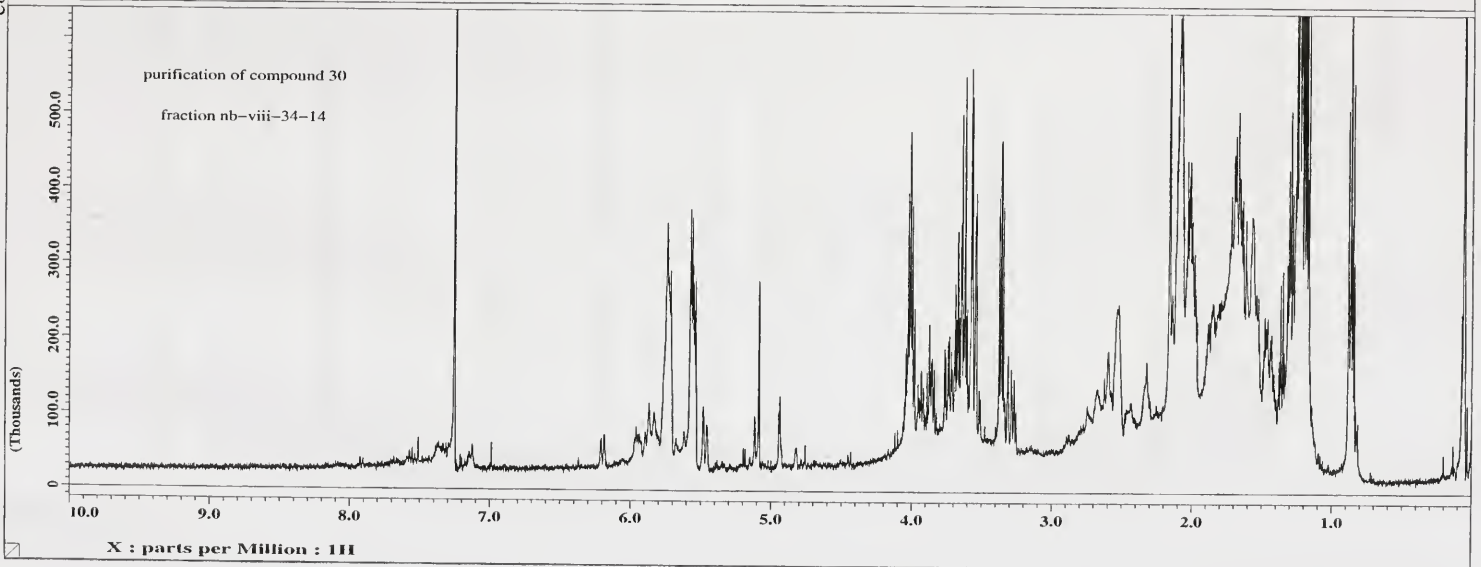

(Millions)
1.0
3.0
Y : parts per Million : 13C
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H
HSQC
compound 29
HO
0
10.0
20.0
30.0
40.0
(Millions)


(Millions)
1.0
3.0
Y : parts per Million : 13C
117.0
119.0
121.0
123.0
125.0
127.0
129.0
131.0
133.0
135.0
137.0
139.0
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
X : parts per Million : 1H
HSQC
compound 29
HO
O
O
0
10.0
20.0
30.0
40.0
(Millions)


compound 29
(Millions)
X : parts per Million : 1H


crude material
compound 30
(Millions)
X : parts per Million : 1H


purification of compound 30
fraction nb–viii–34–13
HO
(Millions)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H


purification of compound 30
fraction nb–viii–34–14
(Thousands)
0
100.0
200.0
300.0
400.0
500.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
X : parts per Million : 1H

Unsuccessful Birch Reductions

Synthetic Scheme 1:

28 - To a stirred solution of phthalide (0.3 g, 2.24 mmol), NH_4OAc (0.19 g, 2.46 mmol), and THF (25 mL) at –78 °C was added NH_3 (*ca.* 50 mL), followed by potassium metal (*ca.* 0.18 g, 4.70 mmol). The rbf was removed from the ice bath and was allowed to warm up for 1 h. The NH_3 evaporated off, and any remaining NH_3 was removed via an H_2O aspirator. The reaction was quenched with 0.3 M NH_4OAc and the THF was removed *in vacuo*. The solution was transferred to a separatory funnel, diluted with EtOAc and the aqueous layer acidified with 3 M HCl to pH ~1. The organic layer was rinsed with saturated sodium bicarbonate, saturated brine, dried using Na_2SO_4, and concentrated *in vacuo*.

28 - To a stirred solution of phthalide (0.3 g, 2.24 mmol) and *i*-PrOH (0.19 mL, 2.46 mmol) at –78 °C was added NH_3 (*ca.* 22 mL), followed by Na^o (*ca.* 0.52 g, 11.2 mmol). The solution was warmed to –40 °C, and immediately cooled to –78 °C, and quenched with NH_4Cl followed by H_2O (15 mL) until the blue color dissipated. The NH_3 was removed with an H_2O aspirator, and the solution was transferred to separatory funnel and diluted with EtOAc. The aqueous layer was acidified to pH 3 with 3 M HCl. The aqueous layer was rinsed with EtOAc (2 x 20 mL). The organic layers were combined, rinsed with saturated sodium bicarbonate, saturated brine, dried, and concentrated *in vacuo*.

28 - To a stirred solution of phthalide (0.14 g, 1.04 mmol) and *i*-PrOH (0.38 mL, 5.2 mmol) at –78 °C was added NH_3 (ca. 35 mL), followed by Na^o (*ca.* 0.38 g, 16.64 mmol). The solution was warmed to –50 °C, maintained at –50 °C for 5 h, then quenched with NH_4Cl followed by H_2O until the blue dissipated. The NH_3 was removed with an H_2O aspirator, and solution was transferred to a separatory funnel and diluted with EtOAc (30 mL). The aqueous layer was

acidified to pH 1 with 3 M HCl, and then rinsed with EtOAc (2 x 30 mL). The organic layers were combined and rinsed with saturated brine until the pH of aq. layer was neutral, and then dried, and concentrated *in vacuo*. The solution was green but would turn yellowish-brown overnight.

Synthetic Scheme 2:

17 - To a stirred solution of benzylidenephthalide (1 g, 4.51 mmol), NH_4OAc (0.39 g, 4.96 mmol), and THF (50 mL) at –78 °C was added NH_3 (*ca.* 100 mL), followed by Na^o (*ca.* 0.22 g, 9.46 mmol). The rbf was warmed to –49 °C, then cooled to –78 °C and quenched with NH_4Cl followed by H_2O. The NH_3 was removed with an H_2O aspirator, then the THF was removed *in vacuo* and the solution was transferred to a separatory funnel and diluted with EtOAc. The aqueous layer acidified to pH 1 with 3 M HCl. The aqueous layer was rinsed EtOAc (2 x 50 mL). The organic layers combined, rinsed with saturated sodium bicarbonate, saturated brine, dried, and concentrated *in vacuo*.

Unknown Compound – To a stirred solution of benzylidenephthalide (2 g, 9.01 mmol) and *i*-PrOH (0.76 mL, 9.91 mmol) was added NH_3 (*ca.* 90 mL) followed by Na^o (2.07 g, 90.1 mmol) at –78 °C. The solution was warmed to –40 °C, maintained at –40 °C for five minutes, then lowered to –78 °C and quenched with a concentrated NH_4Cl and H_2O solution until the blue color dissipated. The solution was diluted with EtOAc, transferred to a sep. funnel, and 3 M HCl was added until the aqueous layer was neutral. The organic layer rinsed with saturated sodium bicarbonate, saturated brine, dried, and concentrated *in vacuo*. Crude material was chromatographed with 1:2 Hex/EtOAc ($R_f = 0.52$) to afford a brown-rust liquid.[11]

Synthetic Scheme 3:

3(1-hydroxyethyl)-3,5-dihydrophthalide (30) - To a stirred solution of **29** (0.20 g, 1.12 mmol) and *i*-PrOH (0.43 mL, 5.62 mmol) at –78 °C was added NH_3 (*ca.* 38 mL), followed by Na^o (*ca.* 0.41 g, 17.98 mmol). The solution was warmed to and maintained at –50 °C for 2.5 h. The reaction was cooled to –78 °C, then warmed to –50 °C and maintained for 1 h, then quenched with NH_4Cl followed by H_2O until the blue color dissipated. The NH_3 was removed with an H_2O aspirator, and the solution was transferred to a separatory funnel and diluted with EtOAc. The aqueous layer was acidified to pH 1 with 3 M HCl and rinsed with EtOAc (2 x 100). The organic layers were combined, rinsed with saturated brine until the pH of aq. layer was neutral, dried, and concentrated *in vacuo*. $R_f = 0.36$ in 1:2 acetone/pet. Ether.

A-37